



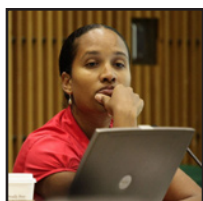
October 2010

NIEHS Spotlight



[NIH to launch Gulf oil spill health study](#)

The National Institutes of Health will launch a multi-year study this fall to look at the potential health effects from the oil spill in the Gulf region.



[Council meeting marks progress with initiatives](#)

The fall meeting of the NIEHS Council featured updates on some of the Institute's major high-profile efforts.



[Birnbaum testifies on heart disease and Agent Orange](#)

NIEHS/NTP Director Linda Birnbaum, Ph.D., entered the national conversation on Vietnam-era exposure to dioxin in Agent Orange.



[NIEHS participates in cookstove initiative](#) Video

NIEHS is one of several NIH institutes and centers participating in the Global Alliance for Clean Cookstoves.



[Leading scientists participate in congressional briefing](#)

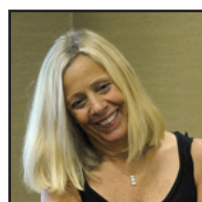
NIEHS/NTP Director Linda Birnbaum, Ph.D., participated in a congressional briefing on endocrine disruption.

Science Notebook



[The involvement of Mullerian Inhibiting Substance in ovarian cancer](#)

According to Patricia K. Donahoe, M.D., a protein involved in human sex determination can play a role in treating cancer.



[New BPA research helps fill research gaps](#)

Barely a year after NIEHS announced \$30 million in funding for research on BPA, new grantee findings are already emerging.



[JBC selects NIEHS study as paper of the week](#)

A study from the NIEHS Mitochondrial DNA Replication Group was chosen as The Journal of Biological Chemistry Paper of the Week.



[Council hears two science talks at fall meeting](#)

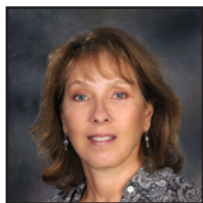
Members enjoyed presentations by grantee Sven-Eric Jordt, Ph.D., and NIEHS Principal Investigator Mike Resnick, Ph.D.



[Evaluating the science on cell phone safety](#) Video

Experts shared their views on the status of current science regarding cell phone safety, as well as the need for better designed studies.

NIEHS Spotlight



[Foundation commits \\$2M more to asthma study](#)

The MCAN will commit \$2 million to sustain a successful program that was led by NIEHS from 2006 to 2010.



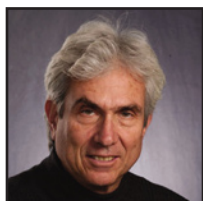
[NIEHS to fund \\$36 million in worker safety training](#)

The NIEHS is awarding \$36 million in grants to 20 organizations that develop safety and health training for workers.



[BPA grantee honored with Heinz Award](#)

Veteran NIEHS grantee Fred vom Saal, Ph.D., received one of the nation's most prestigious public service awards.



[NIEHS-funded investigator awarded Harvey Prize](#)

Grantee Michael Karin, Ph.D., has been awarded the 2010 Harvey Prize in human health by Israel's premier institute of technology.



[First steps for future epidemiologists begin at NIEHS](#)

Two postbaccalaureate fellows credit their training at NIEHS with helping them gain admission to a top U.S. public health school.



[Packenham to be honored for career achievement](#)

NIEHS scientist Joan Packenham, Ph.D., is the winner of a 2010 National Women of Color Award.

Science Notebook



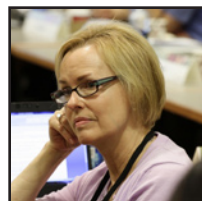
[BPA researchers and regulators meet for update and integration](#)

NIEHS grantees and government scientists gathered Sept. 21-22 at NIEHS to update their research efforts on bisphenol A.



[Regulation of cellular genotoxic response](#)

Yoshiaki Tsuji, Ph.D., shared his new findings on the ways genotoxic stresses influence disease.



[New opportunities in autism research](#)

Researchers and advocates came together Sept. 8 to offer new strategies and opportunities for progress in autism research.



[Expert panel examines autoimmunity research](#)

An NIEHS meeting in Durham, N.C. Sept. 7-8 brought together an interdisciplinary group of experts to evaluate the state of the science.



[New eye safety test methods proposed by interagency group](#)

Federal regulatory agencies will consider adopting new test methods and strategies applicable to safety testing.



[European Teratology Society honors NIEHS-led research](#)

A study funded by an interagency agreement between NIEHS and the FDA was honored as Paper of the Year at annual meeting.

NIEHS Spotlight



[NIEHS-funded trainee receives peace grant](#) Video

Barbara Kowalczyk, co-founder of the Center for Foodborne Illness, will receive the LennonOno Grant For Peace 2010.



[NIEHS Public Health Service officers promoted](#)

Three NIEHS employees are among the U.S. Public Health Service officers promoted this year.



[NIEHS remembers Jenny Pronczuk de Garbino](#)

Friends and colleagues at NIEHS were saddened by news of the death of a global and children's health champion.



[NICEATM convenes international workshop on vaccine safety testing](#)

Nearly 200 scientists from around the world met for an international workshop in Bethesda, Md. on alternative testing methods.



[Institute celebrates postdoctoral fellows](#)

NIEHS recognized its 225 postdoctoral fellows during a celebration of the second annual National Postdoc Appreciation Day Sept. 24.

Science Notebook



[This month in EHP](#)

The October issue of Environmental Health Perspectives is the journal's 13th annual Children's Health Issue.



[Steven Zeisel to give Hans L. Falk Memorial Lecture](#)

Zeisel will address nutrigenomics, estrogen, and environmental chemicals in studies of the dietary requirement for choline.

Extramural Research

[Extramural papers of the month](#)

- [Amplifying stem cells](#)
- [Low dose BPA alters gene expression in the fetal mouse ovary](#)
- [Common genetic variants associated with blood lipids](#)
- [Charlotte, NC light rail transit use reduces obesity risk](#)

Intramural Research

[Intramural papers of the month](#)

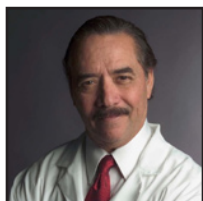
- [Estrogen increases chemical uptake by brain](#)
- [Base damage of single-stranded DNA intermediate causes localized hyper-mutability in budding yeast](#)
- [Genetic biomarkers for early diagnosis of lung cancer](#)
- [Eosinophil peroxidase reacts with sulfite to form protein radicals](#)

Inside the Institute



[NIEHS celebrates Women's Equality Day](#)

The long struggle for equal voting rights for women was at center stage Aug. 26 in a presentation by Noreen Gordon.



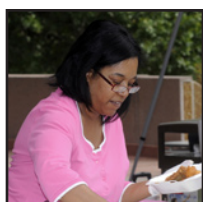
[Exploring the origins of American medicine](#) Video

NIH celebrated Hispanic heritage Sept. 21 with an engaging talk by Eloy Rodriguez, Ph.D., a specialist in ethnobotanical medicine.



[Employees honored for years of service](#)

According to Director Linda Birnbaum, Ph.D., NIEHS honored a total of 1,110 years of service at the second annual celebration.



[Generations at Work Celebration spotlights families](#)

The Generations at Work Celebration featured 29 display tables and the popular Blacks In Government Annual Fish Fry.

Calendar of Upcoming Events

- **Oct. 4** in Rodbell Auditorium, 11:00 a.m.-12:30 p.m. — Falk Lecture Seminar Series with Steven Zeisel, M.D., Ph.D., speaking on “Nutrigenomics, Estrogen, and Environmental Chemicals Influence the Dietary Requirement for Choline”
- **Oct. 7** in Rodbell Auditorium, 12:00-5:00 p.m. — North Carolina Society of Toxicology Fall Meeting
- **Oct. 12** in Rodbell C, 10:00 a.m.-12:00 p.m. — Invited lecture on “Understanding Adverse Events Using Genome Level and Expression Data: Are Canonical Toxicity Profiles a Predictive Possibility?” by James Flynn, Ph.D.
- **Oct. 13** in Rodbell A, 1:30-3:30 p.m. — Hispanic Heritage Month Celebration with Ileana Herrell, Ph.D.
- **Oct. 15 (Offsite Event)** at the Sheraton Imperial Hotel and Convention Center in RTP, 8:00 a.m.-5:00 p.m. — Genetics and Environmental Mutagenesis Society [Fall Annual Meeting 2010](#), “Deep Sequencing, Regulation, and Cancer”
- **Oct. 19-21 (Offsite Event)** at the University of Louisville, Ky., 8:00 a.m.-5:00 p.m. — [2010 NIEHS Center Directors Meeting](#)
- **Oct. 20 (Offsite Event)** at the National Center for Environmental Health Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention, Atlanta, Ga., 10:00-11:30 am — Agency for Toxic Substances and Disease Registry Seminar Series, featuring James Tiedje, Ph.D., exploring “Advances in Dioxin Bioavailability and Biodegradation in Environmental Matrices”
- **Oct. 20** at the NIEHS softball field, 2:00-4:00 p.m. — NIEHS Inter-Division Softball Competition
- **Oct. 21** in Rall B450, 10:00 a.m.-11:00 a.m. — Laboratory of Molecular Carcinogenesis Seminar Series presentation on “Inflammation and Colorectal Cancer: Should We Pay More Attention to the Microbiome?” by Cristian Jobin, Ph.D.
- **Oct. 25-26** in Rodbell Auditorium, 8:30 a.m.-5:00 p.m. — Worker Education and Training Program [Fall 2010 Awardee Meeting and Workshop](#)
- **Oct. 27** in Rodbell Auditorium, 10:00-11:30 a.m. — Keystone Science Seminar Series, speaker and topic TBA
- View More Events: [NIEHS Public Calendar](#)

NIH to launch Gulf oil spill health study

By Robin Mackar

The National Institutes of Health will launch a multi-year study this fall to look at the potential health effects from the oil spill in the Gulf region. The Gulf Study, announced by NIH Director Francis S. Collins, M.D., Ph.D., in June, is in response to the largest oil spill in U.S. history, caused by the explosion of the Deepwater Horizon offshore drilling oil rig in the Gulf of Mexico. Collins pledged \$10 million in NIH funding for the study's initial phases. Collins asked NIEHS to lead the research project.

BP will provide additional funds for research

To help expedite the launch of the study, BP will contribute an additional \$10 million to NIH for this and other important health research. The BP funding will come through the Gulf of Mexico Research Initiative (GRI). The GRI is a ten-year, \$500 million independent research program established by BP to better understand and mitigate the environmental and potential health effects of the Gulf spill. The NIH will have full autonomy regarding the distribution of the \$10 million, with input from external scientific experts in environmental health who are familiar with the Gulf region.



Sandler will lead the first health study of its kind on a major oil spill in U.S. waters. (Photo courtesy of Steve McCaw)

“It was clear to us that we need to begin immediately studying the health of the workers most directly involved in responding to this crisis,” said Collins. “The donation from BP will help speed our work with CDC [Centers for Disease Control and Prevention], EPA [U.S. Environmental Protection Agency], and other federal agencies, academia, as well as state and local partners to carry out this important study.”

The study will focus on exposure to oil and dispersant products, and potential health consequences such as respiratory, neurobehavioral, carcinogenic, and immunological conditions. The study is also expected to evaluate mental health concerns and other oil spill-related stressors such as job loss, family disruption, and financial uncertainties.

Focus on workers, community members, and volunteers

“Cleanup workers are likely to be the most heavily exposed of all population groups in the Gulf Coast region,” said Dale Sandler, Ph.D., chief of the Epidemiology Branch at NIEHS and lead researcher on the study. “We plan to enroll workers with varying levels of exposure. For example, we hope to recruit workers involved in oil burning, skimming and booming, equipment decontamination, wildlife cleanup, and also those with lower exposure such as shoreline cleanup workers. We’ll also recruit some people who completed the worker safety training, but did not have the opportunity to do any cleanup work. They will be our study controls.”

Sandler added, “What we learn from this study may help us prepare for future incidents that put communities at risk.”

The current focus of NIEHS is to ensure that the Gulf communities most affected by the oil spill have a say in the study's design and implementation, as well as input into future research directions. The NIEHS is hosting webinars and other community engagement activities to obtain input.

“Community involvement and participation is critical to the success of this study,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program.

NIH and the U.S. Department of Health and Human Services have had a continuous presence in the Gulf since the explosion occurred. The NIEHS Worker Education and Training Program (WETP) used its 24 years of experience preparing people for hazardous conditions to contribute to training more than 100,000 workers in the Gulf, so they could safely clean up the oil spill. The WETP also distributed thousands of pocket-sized training booklets in English, Spanish, and Vietnamese, so workers have the information they need to protect themselves. The WETP materials are available [online](#).

(Robin Mackar is News Director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

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Institute of Medicine holds meeting on Gulf Worker Study

About 50 leading scientists gathered in Tampa, Fla. Sept. 21 for an Institute of Medicine (IOM) meeting to finalize the design of the ambitious Gulf Worker Study, which expects to start enrolling subjects next month.

Among the attendees were representatives from NIH and NIEHS who want to take the necessary steps to engage public trust with a well-designed study that will meet expectations of people in impacted communities along the Gulf Coast. NIEHS is also receiving scientific and community input through a series of webinars.

According to a report in the St. Petersburg Times, Collins told fellow participants at the meeting that the Gulf Study is different from most research projects because of the degree of public skepticism, the intense public concern over the issue, and the potential for lawsuits.

Council meeting marks progress with initiatives

By Eddy Ball

The [fall meeting](#) of the National Advisory Environmental Health Sciences Council (NAEHSC) Sept. 1-2 featured updates on some of the Institute's major high-profile efforts, including the Gulf oil spill response, advances in predictive toxicology, and allocation of stimulus funding. In addition to these big-picture reports, members also heard presentations on four concept clearances and other developments taking place since the Council's last meeting in May ([see text box](#)).

Presentations by NIEHS/NTP Director Linda Birnbaum, Ph.D., NTP Associate Director John Bucher, Ph.D., and Interim Director of the Division of Extramural Research and Training (DERT) Gwen Collman, Ph.D., reported on progress of several ongoing initiatives. In addition, two science talks gave members insight into groundbreaking research with strong translational potential from investigators supported by the NIEHS intramural and extramural programs ([see related story](#)).



As Birnbaum turned to the budget, she said, “The answer [to exactly what our budget will be] is we really don’t know. We all expect to be on a continuing resolution until after the election.” (Photo courtesy of Steve McCaw)

Leadership presentations headline day one

After introducing NIEHS Director of Outreach and Education Ericka Reid, Ph.D., Toxicology Liaison Chris Weis, Ph.D., and Acting Associate Director of Management Chris Long and discussing ongoing searches for other members of her leadership team, Birnbaum turned to budget projections for fiscal year 2011. Describing herself as “guardedly optimistic,” she said the comparatively good news is that things will probably not be as bad as they could have been, considering calls from the President and Congress to reduce federal spending. NIEHS, she said, may actually see a 2 to 3 percent increase — not a reduction in dollars, as some government agencies will likely face, but also not enough to keep pace with inflation.



Weis, center, was one of three new members of the NIEHS leadership introduced by Birnbaum. He serves as the liaison to the toxicology community and works out of the Institute's Bethesda office. (Photo courtesy of Steve McCaw)

In her update on the NIEHS Gulf oil spill effort, Birnbaum described the many NIEHS activities in the Gulf and the ambitious Gulf Worker Study announced officially Sept. 7 ([see related story](#)). She noted that of 30 major oil spills, only eight had been studied to any degree in terms of health effects and only one, in Spain, had received long-term follow-up. For this reason, the Gulf Worker Study has tremendous potential for better understanding long-term health effects from worker exposures and responding to such disasters in the future.

The title of the NTP report by Bucher — “Connecting the Dots — Diseases, Genes, HTS Targets” — aptly described his report on the Tox21 multi-agency predictive toxicology initiative, the 12th Report on Carcinogens, and the new directions in activities of the [Center for the Evaluation of Risks to Human Reproduction](#), including a novel design of its workshop on diabetes scheduled for Jan. 11-13. As Tox21 partners enter the second phase of their activities, they have gained a powerful new tool with the purchase of DrugMatrix® database, acquired at what Bucher described as “a fire sale” from former owner Iconix.

When her turn came, Collman treated members to a detailed review thus far of outcomes from funding awarded by NIEHS as part of the American Recovery and Reinvestment Act (ARRA), including a highly successful program of supplements for summer students and science educators that anticipated similar efforts planned by NIH. She also focused on the new NIEHS administrative role in the NIH Research on Research Integrity Program, involving investigation into bias and public trust, with possible expansion into the areas of community engagement and cultural diversity. Finally, Collman discussed the Interagency Breast Cancer and Environmental Research Coordinating Committee, co-led by NIEHS and the National Cancer Institute to help frame a strategic federal research agenda on environmental and genetic factors related to breast cancer ([see related story](#)).



NIEHS legislative liaison Mary Gant, right, joined Director of the Office of Policy, Planning, and Evaluation Sheila Newton, Ph.D., to answer questions about implications for the Institute of pending legislation. (Photo courtesy of Steve McCaw)



Bucher was upbeat in his report on Tox21 and said, “There’s beginning to be some success at identifying ‘fingerprints’ of potential activities that are related to certain chemical types and structural relationships.” (Photo courtesy of Steve McCaw)

Closing out the public portion of the Council meeting was a report by NIEHS Board of Scientific Counselors (BSC) chair [Jack Keene, Ph.D.](#), James B. Duke Professor in the Department of Molecular Genetics and Microbiology at Duke University. Keene described the advisory role of the BSC, explained the evaluation template for laboratories and principal investigators under review, and pointed to challenges facing the intramural program at NIEHS.



Above, University of Rochester Professor Thomas Gasiewicz, Ph.D., concentrated as he listened to the budget report. Gasiewicz was attending his first Council meeting as its newest member. (Photo courtesy of Steve McCaw)



Keene, right, conferred with Collman during the minutes before he took the podium for his report. (Photo courtesy of Steve McCaw)

Highlights of a busy day

- Legislative Report by Director of the Office of Policy, Planning, and Evaluation Sheila Newton, Ph.D.
- Budget Update by Budget Officer Laurie Johnson
- P30 Assessment by Program Analysis Branch Chief Christie Drew, Ph.D.
- Superfund Research Program Strategic Plan by Center for Risk and Integrated Sciences Director Bill Suk, Ph.D.
- Concept Clearance — Statistical, Bioinformatics, and Analytical Methods for Detection of G x E Interactions in Complex Diseases by Program Administrator Kim McAllister, Ph.D.
- Concept Clearance — The Environmental Health Sciences Centralized KnowledgeBase by Program Administrator Elizabeth Maull, Ph.D.
- Concept Clearance — Identification of Biomarkers for Early Detection of Mitochondrial Dysfunction by Program Administrator Daniel Shaughnessy, Ph.D.
- Concept Clearance — Environmental Influences on Transcriptional Regulation by Health Scientist Administrator Lisa Chadwick, Ph.D.

More detailed summaries of Council presentations are available [online](#).

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Birnbaum testifies on heart disease and Agent Orange

By Eddy Ball

NIEHS/NTP Director Linda Birnbaum, Ph.D., entered the national conversation on Vietnam-era exposure to dioxin in Agent Orange and its link to ischemic heart disease (IHD). She joined two other scientists, Secretary of Veterans Affairs (VA) Eric Shinseki, and former Secretary Anthony Principi as witnesses at a hearing on “[VA Disability Compensation: Presumptive Disability Decision-Making](#)” Sept. 23 conducted by the United States Senate Committee on Veterans’ Affairs.

While she maintained scientific objectivity about the level of evidence in studies of dioxin and IHD, Birnbaum testified that exposure to the chemical is associated with alterations in the vascular structure, gene expression, and several other diseases and conditions related to ischemic heart disease.

“There are a number of other risk factors that can influence the development of this disease,” said Birnbaum. “It is also unclear from studies available to us how much risk remains many years after exposure.”

Chaired by Senator Daniel Akaka (D-Hawaii), the committee heard first from Shinseki’s one-person panel on the role of presumptions of service connection in claims for Veterans’ benefits and, in particular, to discuss presumptions established pursuant to the Agent Orange Act of 1991. In his testimony and in response to questions from committee members, Shinseki underscored the government’s commitment to provide Vietnam veterans with treatment and compensation for the health effects of herbicide exposure, including IHD.

Birnbaum was part of panel two and joined Principi, National Heart, Lung, and Blood Institute scientist Diane Bild, M.D., and University of Southern California researcher Jonathan Samet, M.D., who headed the Institute of Medicine (IOM) Committee on Evaluation of the Presumptive Disability Decision-Making Process for Veterans. They spoke on details of IHD and the several factors, including dioxin exposure during service in Vietnam, that increase risk for developing the disease.

“Understanding the role that environmental and occupational exposures play in the development of chronic diseases can be challenging,” Birnbaum explained, “particularly for diseases that have significant risk factors in addition to the chemical exposure.” She reviewed a meta-analysis that she and her colleagues published in 2008, the IOM conclusion that “there is limited or suggestive evidence of an association between Agent Orange or dioxin exposure and ischemic heart disease,” and the ongoing reassessment of dioxin by the U.S. Environmental Protection Agency (EPA).

Following her [testimony](#), Birnbaum was asked by Akaka about the latest EPA evaluation of dioxin’s impact on health. Although she observed that very few studies specifically addressed IHD, she said, “It is clear that ... dioxin can cause heart disease as a consequence.”



Birnbaum has appeared before several Congressional committees and subcommittees as an expert in environmental health and disease caused by environmental exposures. (Photo courtesy of Steve McCaw)

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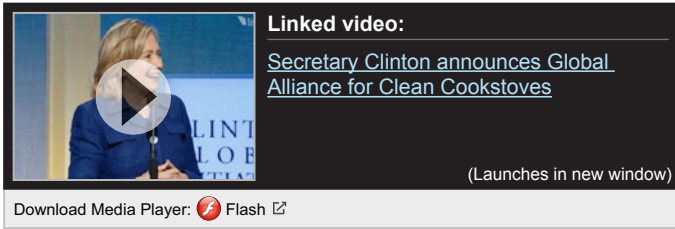
NIEHS participates in cookstove initiative

By Eddy Ball

NIEHS is one of several NIH Institutes and Centers participating in the Global Alliance for Clean Cookstoves, which was launched at a press event in New York City Sept. 21 ([see NIEHS Web page](#)). Keynote speaker at the meeting of the [Clinton Global Initiative \(CGI\)](#), where the Alliance was announced, was Secretary of State Hilary Clinton. Clinton was introduced at the Empowering Girls and Women plenary by President Bill Clinton.



Senior Advisor John Balbus, M.D., above, leads NIEHS participation in the Alliance and works to raise the profile of the Institute on the Bethesda and Washington fronts, as well as nationwide, where NIEHS can have the most impact on public health and policy. (Photo courtesy of Steve McCaw)



“Today we can finally envision a future in which open fires and dirty stoves are replaced by clean, efficient and affordable stoves and fuels all over the world — stoves that still cost as little as \$25. By upgrading these dirty stoves, millions of lives could be saved and improved,” Secretary Clinton told attendees. “Clean stoves could be as transformative as bed nets or vaccines.”

The [Alliance](#) is a new public-private partnership that aims to improve global public health, combat climate change, and improve indoor air quality, especially for women and children, by creating a thriving global market for clean and efficient household cooking solutions. The Alliance is a United Nations Foundation-led initiative to spur the adoption of clean and efficient cookstoves and fuels by 100 million households in the developing world by 2020 — the basis for the Alliance slogan of “100 by 20.”

According to the Alliance, one of the greatest threats facing developing countries and their populations, is the harmful effects of exposure to smoke from indoor fires and inefficient cook stoves used to prepare daily meals. Roughly half of the world’s population – three billion people – rely on these cooking methods causing severe health, economic, and environmental consequences from what Clinton described as a “toxic mix” that kills as many as two million people each year.

A U.S. Department of State [press release](#) described the Alliance as an unprecedented and coordinated effort by the U.S. Department of State, foreign governments, the U.S. Department of Health and Human Services, NIH, the Centers for Disease Control, the U.S. Department of Energy, the U.S. Environmental Protection Agency and the U.S. Agency for International Development to mobilize key financial resources, top experts, and research and development tools. The initial U.S. financial commitment to the Alliance is \$50.82 million over the next five years.

Along with studies on the health effects of indoor air pollution by several NIH Institutes and Centers, NIEHS has invested around \$9 million in leading investigator-initiated health effects research and pioneering intervention studies, such as those conducted by grantee and 2009 Heinz Award winner [Kirk Smith, Ph.D.](#) NIEHS-funded research on cookstoves and indoor air pollution has helped people in the U.S., Guatemala, Ecuador, Nepal, Pakistan, and Ghana.

NIEHS plans to maintain constant funding at approximately \$1.8 million per year in this area. As part of the new Alliance, NIH also plans to host a state-of-the-science conference on cookstoves and indoor air pollution.

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Leading scientists participate in congressional briefing

By Eddy Ball

A group of four distinguished scientists that included NIEHS/NTP Director Linda Birnbaum, Ph.D., participated in a congressional briefing on endocrine disruption in Washington, D.C. Sept. 20. Their audience included members of the U.S. House and Senate hosted by four of the most influential committee and subcommittee chairs from each branch of Congress gathered at the U.S. Capitol Visitor Center.

Titled “Endocrine Disruption: Modern Science Unveils How Chemicals Can Act Like Hormones,” the briefing was jointly sponsored by the [Pew Health Group](#), part of the Pew Charitable Trusts, and the [Endocrine Society](#). Honorary hosts of the event were some of the most environmentally aware leaders in the U.S. Congress:

- Sen. Frank Lautenberg (D-NJ), chairman of the Senate Committee on Environment and Public Works Subcommittee on Superfund, Toxics and Environmental Health
- Rep. Henry Waxman (D-Calif.), chairman of House Committee on Energy and Commerce
- Rep. Bobby Rush (D-Ill), chairman of the House Committee on Energy and Commerce Subcommittee on Commerce, Trade and Consumer Protection
- Rep. Jim Moran (D-Va.), chairman of the House Committee on Appropriations Subcommittee on Interior, Environment and Related Agencies

In addition to Birnbaum, the presenters were Thomas Zoeller, Ph.D., professor in the Department of Biology at the University of Massachusetts Amherst; Louis Guillette Jr., Ph.D., professor in the Department of Obstetrics and Gynecology at the Medical University of South Carolina; and John Peterson Myers, chief scientist and CEO of Environmental Health Sciences.

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During the busy third week of September, Birnbaum was doing the business of NIEHS in Washington on Monday, in Tampa on Wednesday at a meeting about the Gulf oil spill, and again in Washington on Thursday testifying before the United States Senate Committee on Veterans' Affairs. (Photo courtesy of Steve McCaw)

Foundation commits \$2M more to asthma study

By Eddy Ball

The Merck Childhood Asthma Network (MCAN), Inc., will commit \$2 million to sustain a successful program for managing childhood asthma in New Orleans that was led by NIEHS from 2006 to 2010. The new [MCAN](#) grant to Xavier University of Louisiana's Center for Minority Health and Health Disparities Research and Education will support phase two of the [Head-off Environmental Asthma in Louisiana \(HEAL\) Project](#).

Mobilizing resources in response to a public health crisis

In the aftermath of Hurricane Katrina, NIEHS started up the first phase of the project along with researchers at [Tulane University](#), Louisiana State University, and the New Orleans Department of Health. The project was funded by NIEHS, MCAN, and the National Center on Minority Health and Health Disparities (NCMHD). HEAL was one of the largest public-private partnerships ever established to address and support an asthma initiative.

The HEAL study partnered 184 asthmatic children, 4 to 12 years old, and their families with a team of health education specialists and community health workers. The specialists provided education and counseling to caregivers on how to manage their child's asthma in a transformed environment and help them improve the environment at home ([see text box](#)).



*HEAL study investigator Patricia Chulada
(Photo courtesy of Steve McCaw)*

Planning and carrying out a sustainable program

A lead investigator on the HEAL Project was Patricia Chulada, Ph.D., health scientist administrator in the NIEHS Program in Clinical Research, who is currently completing reports on phase one and overseeing data analysis. Chulada attributed the project's success to careful design of the study, meticulous planning of the intervention, and the dedication of the various partners and HEAL scientists. Several of the New Orleans partners in HEAL lost their homes due to Katrina and could identify with HEAL families.

In a draft report on HEAL, Chulada explained, "With HEAL, we combined traditional case-management and environmental interventions from two evidence-based studies — the National Cooperative Inner-City Asthma Study (NCICAS) and the Inner-City Asthma Study (ICAS) — into a 'hybrid' intervention and made modifications to meet the specific needs of post-Katrina families. Our goal was to create a sustainable program for the New Orleans area, as well as a model that could be applied to other natural disaster situations similar to post-Katrina New Orleans."

"Conducting HEAL was very challenging. There was little surviving infrastructure and families were having a difficult time finding adequate housing and just carrying out normal daily activities," Chulada said recently. "HEAL was a great study, and it sets a standard for future projects of its kind. It also created a rich repository of data and samples that researchers will be able to mine for years, as scientists better understand the triggers of asthma and how best to measure them."

Looking ahead to phase two of HEAL

MCAN agreed with Chulada's assessment of the program. As its Aug. 27 press release stated, "The progress for children in the program was positive and cut children's days with symptoms in half, compelling MCAN to pledge nearly \$2 million to continue the successful program."

Speaking of the lessons of HEAL's phase one outcomes, MCAN Executive Director Floyd Malveaux, M.D., Ph.D., added, "There is an undeniable connection between the environment and the health of children with asthma. Effective asthma management must go beyond traditional medical care and include additional interventions to manage the problem, as well as to reduce exposure to the specific environmental triggers known to exacerbate a child's asthma."

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Creating a model for intervention on the home front

The HEAL home environmental evaluation was one of the most comprehensive ever conducted in a study of this type. Specialists visited caregivers and children in their homes, and helped them remediate asthma risk factors and triggers. This intervention was tailored to the results of a home environmental evaluation and the children's skin sensitivities.

Specialized field technicians periodically inspected the children's homes, focusing moisture, allergens, and other toxic agents. They collected numerous air, dust, and filter samples from multiple rooms to be used in measuring a broad range of suspected allergens with a special focus on mold. Results from the home evaluation were used in conjunction with the children's asthma symptoms and skin sensitivities to both evaluate the effectiveness of the education specialists and help HEAL scientists characterize post-Katrina exposures.

Phase one of HEAL showed the value of a comprehensive home-front intervention. Over a one-year period childhood maximum symptom days, measured over two-week periods, were reduced by nearly 50 percent.

NIEHS to fund \$36 million in worker safety training

By Ed Kang

The National Institute of Environmental Health Sciences (NIEHS) is awarding \$36 million in grants to 20 organizations that develop safety and health training for workers involved in hazardous waste operations and transportation, environmental restoration of contaminated facilities, and chemical emergency response. These training programs can receive annual funding for up to five years (see [press release](#) for list of grantees).

Five awardees in the Gulf Coast region will use the money to continue ongoing safety and health training activities in response to the Deepwater Horizon oil spill. Oil cleanup experts and hazardous material trainers are providing curricula review and assistance with quality assurance to BP, while also delivering classroom and onsite safety and health training. Awardees will also be analyzing and documenting the effectiveness of oil spill response training to prepare for future efforts.



WETP Director Chip Hughes (Photo courtesy of Steve McCaw)

“For 33 years, workers trained by NIEHS programs have been among the first to respond to disasters, including the Sept. 11 attacks, Hurricane Katrina, and the Gulf oil spill,” said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. “These grants will ensure that those on the front lines and in the greatest danger have the skills they need to protect themselves, their communities, and the environment.”

“We have developed a strong network of non-profit organizations that are committed to safety,” said Chip Hughes, whose NIEHS Worker Education and Training Program (WETP) administers the funding. “Since 1987, more than two million hazardous waste workers and emergency responders have received potentially life-saving training.”

The Superfund Amendments and Reauthorization Act gave NIEHS the responsibility for initiating the Worker Education and Training Program funded by grants. The primary objective of this program is to fund non-profit organizations with a demonstrated track record of providing occupational safety and health education in developing and delivering high quality training to workers who are involved in handling hazardous waste or in responding to emergency releases of hazardous materials.

More information on the awards and the NIEHS Worker Education and Training Program can be found [online](#).

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

NIEHS WETP provided awardees funds from multiple program areas:

- The Hazardous Waste Worker Training Program provides occupational safety and health training for workers engaged in hazardous waste removal and containment or chemical emergency response. During 2010-2011, NIEHS will award a total of \$20.6 million to 20 organizations.
- The Nuclear Weapons Cleanup Training Program is a partnership with the U.S. Department of Energy (DOE) to train workers in environmental restoration, waste treatment, and emergency response activities at DOE’s nuclear weapons facilities. During 2010-2011, NIEHS will award a total of \$9.6 million to eight organizations.
- The Minority Worker Training Program delivers comprehensive training to disadvantaged urban youth to prepare them for employment in the environmental restoration and hazardous materials fields. During 2010-2011, NIEHS will award a total of \$3.5 million to four organizations.
- The Hazmat Disaster Preparedness Training Program fosters the development of training programs for the purpose of preparing a cadre of experienced workers for prevention and response during natural and man-made disasters. During 2010-2011, NIEHS will award a total of \$2.3 million to 10 organizations.

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BPA grantee honored with Heinz Award

By Eddy Ball

Veteran NIEHS [grantee](#) Fred vom Saal, Ph.D., received one of the nation’s most prestigious public service awards Sept. 21 when Teresa Heinz and the [Heinz Family Foundation](#) announced the recipients of the 16th annual Heinz Awards.

As one of this year’s ten winners, [vom Saal](#) is being recognized by the foundation for his contributions to addressing global change in unique, innovative, and powerful ways. Heinz Award winners receive a gold medal with an image of the late Senator John Heinz and a \$100,000 cash award.

Since 1997, vom Saal has been investigating the health effects of the chemical bisphenol A (BPA) and is credited with uncovering health concerns about exposure to the chemical in consumer products at levels previously considered safe. In its [press release](#), the foundation praised vom Saal's "groundbreaking research findings [that] have significantly impacted approaches used to study the health effects of environmental chemicals and public health policy" (see text box).

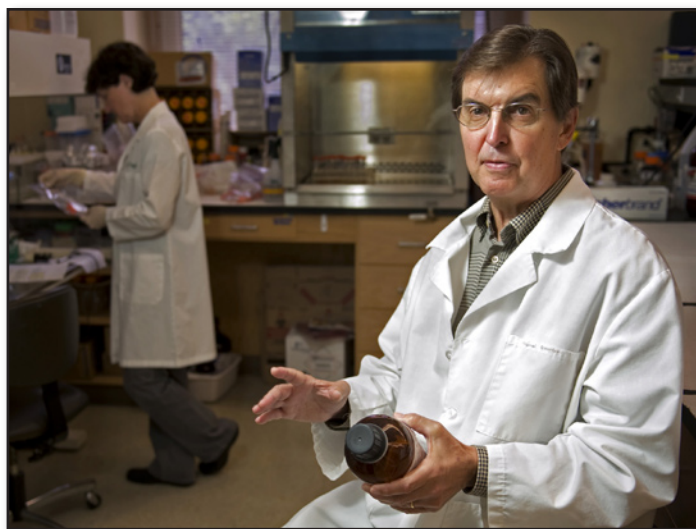
The announcement also pointed to how his research and testimony about BPA have impacted banning or regulating BPA in Canada, Europe, Japan, and some parts of the U.S. Foundation chairman Teresa Heinz was quoted as saying, "His research has prompted policymakers and corporations to evaluate the toll BPA is having on our health."

vom Saal is the Curators Professor of Biological Sciences and head of the [Endocrine Disruptors Group](#) at the University of Missouri–Columbia. The Heinz is the latest in a series of awards and recognition for vom Saal's research into the effects on fetal development of endogenous sex hormones, naturally occurring estrogenic chemicals in food, and estrogenic manmade chemicals in consumer products.

He is an elected member of the American Association for the Advancement of Science and honorary member of the Italian Academy of Sciences. His scientific discoveries also won him the Upstream Award from the Jennifer Altman Foundation and the Millennium Award from the Indian Institute for a Sustainable Future.

This year's winners will receive their awards Nov. 15 at a ceremony in Washington, D.C. Two other scientists honored this year also have ties to NIEHS — Terrence Collins, Ph.D., of Carnegie Mellon University, honored for using green chemistry to detoxify hazardous chemicals and training the next generation of scientists; and Lynn Goldman, M.D., of George Washington University, recognized for promoting regulation of dangerous chemicals and expanding citizens' right to know about pollution in their communities. Goldman has served as an advisor to the National Toxicology Program and participated in many NIEHS-sponsored meetings and seminars.

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When his award was announced, vom Saal, shown above in his lab, was attending a BPA grantees meeting at NIEHS. He readily acknowledges the importance of the funding he has received from NIEHS to pursue his groundbreaking investigations. (Photo courtesy of the Heinz Family Foundation)

A tribute from the Heinz Family Foundation

In its announcement of the award, the Heinz Family Foundation praised vom Saal for his science and his tireless advocacy of measures to limit exposures to endocrine-disrupting compounds:

"Building upon an already distinguished career in basic reproductive biology, Dr. vom Saal discovered unexpected health problems linked to exposure to common chemicals in every day products such as bisphenol A (BPA), a widely-used ingredient in consumer products. Dr. vom Saal's work has been crucial to opening new questions about the safety of many chemicals in widespread use, which had been thought safe based on traditional methods used in toxicology.

His research challenges health agencies around the world to use 21st century biomedical science in assessing the risks posed by environmental chemicals. While some regulatory agencies have taken action, others have been slow to respond. The market, however, has moved quickly due to consumers demanding alternatives to materials that science reveals may be harmful."

NIEHS-funded investigator awarded Harvey Prize

By Eddy Ball

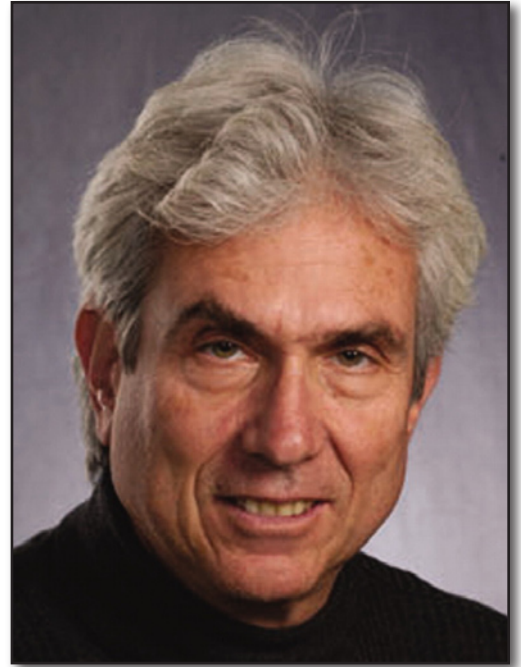
NIEHS [grantee](#) Michael Karin, Ph.D., has been awarded the 2010 Harvey Prize in human health by the Technion, Israel's premier institute of technology, according to a [press release](#) issued by the University of California, San Diego (UCSD). The prestigious prize, which includes a \$75,000 cash award, honors Karin's seminal research linking obesity, inflammation, and cancer.

The [Harvey Prize](#) has been awarded annually since 1972 to recipients in human health, in science and technology, and for contributions to peace in the Middle East. It is named after Leo M. Harvey, an American industrialist who established the prize fund. To date, 13 Harvey Prize laureates have gone on to win a Nobel Prize.

A distinguished professor of pharmacology and pathology at the UCSD School of Medicine, [Karin](#) is also leader of a UCSD Superfund [research project](#). His Harvey is the latest in a long list of honors he has received for his research (see text box).

In their announcement of the award, the judges noted Karin's "pioneering contributions" to the deciphering of the molecular mechanism used by mammalian cells to react to cytokines, adverse environmental conditions, and various pathogens.

"These discoveries," the judges said, "led to the identification of new target proteins that have recently been used to develop new medications for preventing and treating various malignant tumors."



*Harvey Prize winner Michael Karin
(Photo courtesy of UCSD)*

Karin's research interests

Karin's lab has identified cytokines and responding transcription factors involved in cancer. Drugs that inhibit activation of a key transcription factor called STAT3 are in development and slated for clinical trials soon. Karin and colleagues have long been interested in how cells and biological systems function at the molecular level, in both healthy and stressed or diseased states. The research has broad, practical implications and applications, notably in such conditions as obesity and cancer.

"In addition to its well-known contribution to cardiovascular disease and metabolic disorders, such as type II diabetes, obesity has been found to increase cancer risk," said Karin. "Of all cancers, the one most affected by obesity is liver cancer, the third leading cause of cancer-related deaths worldwide. Our work has shown that obesity promotes the development of liver cancer through inflammatory mechanisms similar to those we elucidated earlier in colorectal cancer, another very common inflammation-promoted cancer."

Karin has received numerous awards including the Ernst Oppenheimer Award for Excellence in Research from the Endocrine Society, The Herman Beerman Lectureship from the Society for Investigative Dermatology, C.E.R.I.E.S. Research Award for Physiology or Biology of the Skin, The Grossman Lectureship from the American Gastroenterological Association, and an American Cancer Society Research Professorship in 1999. Karin was elected to the National Academy of Sciences in 2005. He also serves on several advisory boards and was cofounder of Signal Pharmaceuticals (currently Celgene Corporation).

Karin will accept the Harvey Prize at a ceremony at the Technion in Haifa, Israel on March 15, along with [Alexander Polyakov, Ph.D.](#), a theoretical physicist at Princeton University awarded the 2010 Harvey Prize for science and technology.

NIEHS has funded Karin's grant, "Stress Signaling Pathways in Toxicity and Disease," since 1993. The grant is currently administered by NIEHS Program Administrator David Balshaw, Ph.D. Karin also receives support from the [UCSD Superfund Research Program](#), funded by an NIEHS [grant](#) administered by Health Scientist Administrator Heather Henry, Ph.D.

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First steps for future epidemiologists begin at NIEHS

By Sophie Bolick

Former NIEHS postbaccalaureate fellows Cynthia Lin and Alexandra (Lexie) White are several weeks into the Ph.D. program in Epidemiology at the University of North Carolina at Chapel Hill. They credit their training at NIEHS with helping them focus their research interests and gain admission to one of the top public health schools in the country, as ranked by U.S. News and World Report.

Lin, a graduate of the University of Chicago, began exploring epidemiology as a career option while still an undergraduate student. The summer before her senior year, she worked on a project at the National Cancer Institute studying the relationship between intestinal parasite infections and Kaposi's sarcoma in Uganda. The summer after graduating, she spent time working as a policy intern at Taiwan's equivalent of the Centers for Disease Control.

White, a graduate of Kenyon College whose first exposure to epidemiology came during her year of training at NIEHS, took her Intramural Research Training Award fellowship time to decide whether to pursue a Ph.D. in basic medical science or epidemiology. "I was open-minded to what graduate programs I was interested in. Ultimately, I decided to focus on epidemiology." She contributed to several ongoing projects within the Molecular and Genetic Epidemiology Group, headed by Principal Investigator [Jack Taylor, M.D., Ph.D.](#)



Lin, who holds a B.A. in Public Policy Studies, intends a career bridging her experiences in policy and epidemiology. (Photo courtesy of Steve McCaw)

Lin spent two years in her fellowship as a special volunteer contributing to several ongoing studies in the Epidemiology Branch headed by Principal Investigator [Dale Sandler, Ph.D.](#) "Dr. Sandler gave me the opportunity to work on several small projects, which exposed me to different types of studies and methods," she explained. "My experience at NIEHS helped me develop my research interests and I plan to concentrate my graduate work in the field of environmental epidemiology."

While there are only between 10 and 15 postbaccalaureate fellows at NIEHS at any one time, they play an important role in the NIEHS Intramural program. "They serve as good role models for our summer interns, and they remind our postdoctoral fellows, who can often become narrowly focused on an individual project,

how exciting and fun research can and should always be,” commented Diane Klotz, Ph.D., director of the NIEHS [Office of Fellows’ Career Development](#). “Postbaccalaureate fellows are just at the point of making decisions about their scientific futures and what type of education they will continue to pursue, and this motivates them to be productive while they are at the NIEHS.”

(Sophie Bolick, Ph.D., is a postdoctoral fellow in the Molecular and Genetic Epidemiology Group in the Laboratory of Molecular Carcinogenesis.)

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*White foresees a career in public health involving aspects of health disparities research and women’s health, specifically in underserved communities.
(Photo courtesy of Alexandra White)*

Packenham to be honored for career achievement

By Eddy Ball

NIEHS scientist Joan Packenham, Ph.D., is the winner of a 2010 National Women of Color Award in the category of Career Achievement – Government. Packenham, who is director of the Institute’s Office of Human Research Compliance, will join 27 other leading women in science, technology, engineering, and mathematics (STEM) careers honored at the 15th annual [Women of Color \(WOC\) STEM Conference](#) Oct. 30 in Dallas.

Hosted by the [Career Communications Group, Inc.](#) Women of Color Magazine and IBM, the conference is focused on the development of minority women in STEM careers and ensures that the superior achievements and importance of these outstanding women are highly visible to all conference participants. WOC honors achievement in several areas of government, industry, military, research, and management, for professional development, career achievement, and leadership.

In his letter of nomination, Packenham’s supervisor, Acting Clinical Director Darryl Zeldin, M.D., praised her for being “a visionary in her leadership in developing the infrastructure and necessary components for a successful human research protection program (HRPP) for the NIEHS. In addition,” he continued, “under Joan’s leadership, NIEHS has increased visibility on the NIH main campus, and the NIEHS HRPP serves as one of the model programs for NIH, as the organization prepares for national accreditation of its Human Research Protection Program.”

As Zeldin explained in his nomination, Packenham has achieved several firsts in her scientific education at the University of North Carolina at Chapel Hill, postdoctoral training at NIEHS, and career at the Institute. “Joan also gives back to the community at-large through her educational outreach activities,” he added, pointing to the summer science camp her sorority holds each year for Durham school children.

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*Award winner Joan Packenham
(Photo courtesy of Steve McCaw)*

NIEHS-funded trainee receives peace grant

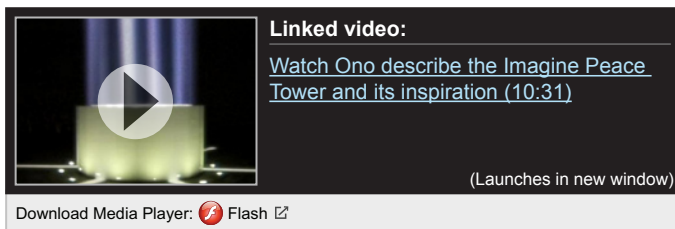
By Melissa Kerr

Barbara Kowalczyk, co-founder of the [Center for Foodborne Illness Research and Prevention \(CFI\)](#), will receive the [LennonOno Grant For Peace 2010](#) on Oct. 9 for her efforts to improve food safety. The grant was started by Yoko Ono in 2002 and is given in honor of the peace activism ideals of John Lennon. Kowalczyk is supported by an NIEHS training grant during her studies at the University of Cincinnati.

“The [LennonOno] Grant focuses on the issues where healing is needed,” Ono explained in 2002 when the Grant was initiated. The honor is bestowed biennially and awards two recipients \$50,000. This year marks what would have been John Lennon’s 70th birthday, and Ono has decided to grant four awards to honor the occasion.



*LennonOno Grant for Peace 2010 winner
Barbara Kowalczyk (Photo courtesy of
Barbara Kowalczyk)*



The presentation of these awards will be in conjunction with the lighting of the Imagine Peace Tower located on the island of Videy near the Icelandic capital of Reykjavik. Kowalczyk joins the ranks of esteemed peace advocates, such as investigative journalist Seymour Hersh, Israeli artist Zvi Goldstein, and Palestinian artist Khalil Rabah.

“I am very honored to have received the LennonOno Grant for Peace,” said Kowalczyk. “This award will help focus international attention on the fundamental importance of food safety to a healthy civil society and highlights the need for a holistic and sustainable approach to food and food safety that integrates human, animal, and environmental health.”

Food safety issue struck home for prize winner

According to the Centers for Disease Control and Prevention, every year an estimated 76 million Americans become ill from foodborne bacteria, 325,000 are hospitalized, and 5,000 die. With *E. coli* alone, about 70,000 infections are reported yearly resulting in about 60 deaths. Unfortunately, these grim statistics were played out in the life of Kowalczyk’s own two-year-old son, Kevin.

In 2001, after returning home from a family vacation, Kevin suffered from a fever and gastrointestinal symptoms. After a few days of worsening symptoms, he was admitted to the hospital where tests proved he had contracted a very aggressive strain of the bacteria *E. coli* O157:H7. With no treatments or cure available, Kevin’s health declined until he died on Aug. 11, 2001, only twelve days after his symptoms started.

Feeling ignored by a lack of local, state, and federal governmental response, Kowalczyk began teaching others of the dangers of foodborne illnesses. She volunteered as a consumer advocate, served on a number of boards

and committees on food safety, and gave several presentations including testifying before policymakers in Washington, D.C. She recently participated in the documentary film, “Food, Inc.,” and is currently pursuing a doctorate in environmental health with a focus on epidemiology and biostatistics at the University of Cincinnati. Along with her mother, she founded the Center, a non-profit organization dedicated to improving public health by preventing illness and death due to foodborne disease, through research, education, and advocacy.

“I think Ms. Ono has recognized — as many others have — that food sustainability and food safety play a vital role in global health and world peace,” said Kowalczyk. With her family along to witness the event, Kowalczyk and the other honorees will receive the awards on Oct. 9 and join Ono in lighting the Imagine Peace Tower that will remain lit until Dec. 8, the anniversary of Lennon’s death.

Kowalczyk is also a contender in the [Huffington Post Game Changers](#) series. According to the website, the series highlights innovators within different categories, and Kowalczyk is one of the names listed as an “Ultimate Food Game Changer.”

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)

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Recipients of the LennonOno Grant for Peace 2010

- Filmmaker Josh Fox wrote and directed the documentary feature film [Gasland](#) in 2010. Josh’s work is known for its mix of gripping narrative, heightened imagery and its commitment to socially conscious themes and subjects.
- Barbara Kowalczyk was propelled into food safety advocacy in 2001, when her two-year-old son, Kevin, died after suffering an E. coli infection from tainted food. Kowalczyk and her mother, Patricia Buck, created [CFI](#), a national non-profit organization committed to improving public health by preventing foodborne illness through research, education, advocacy, and service.
- Author Michael Pollan has been writing books and articles about the places where nature and culture intersect: on our plates, in our farms and gardens, and in the built environment. He is the author of numerous best sellers, most recently *Food Rules: An Eater’s Manual*.
- Author, poet, and activist Alice Walker is known for her brave stance against racism, sexism, and human rights issues. In 2009, she traveled to Gaza along with a group of 60 other female activists from the anti-war group Code Pink to oppose the controversial blockade and violence against Gaza by Israel and Egypt. Her book *Overcoming Speechlessness* documents her experiences in Gaza and abroad.

NIEHS Public Health Service officers promoted

By Eddy Ball

Three NIEHS employees are among the [U.S. Public Health Service](#) Commissioned Corps officers promoted this year at the 8th Annual NIH Promotion Ceremony on the NIH campus in Bethesda, Md. Lieutenant Commander (LCDR) Lindia Engram, Commander (CDR) Debra King, and LCDR John McLamb were honored for their service with promotions.

“The Commissioned Corps of the U.S. Public Health Service [PHS] is a unique and integral part of HHS,” said NIEHS/NTP Director Linda Birnbaum, Ph.D. “We are proud to have several PHS officers here at NIEHS. ... Please join me in congratulating our NIEHS officers for their hard work and dedication to our nation’s health.” Birnbaum also thanked the employees’ supervisors for their help with the promotion packages.

Engram is an occupational health nurse in the NIEHS Health and Safety Branch, King is a medical technologist in the NTP Clinical Pathology Group, and McLamb is a health physicist in the NIEHS Health and Safety Branch.

The Commissioned Corps is an elite uniformed all-officer organization. The Corps is made up of more than 6,000 full-time, well-trained, highly qualified public health professionals dedicated to delivering the nation’s public health promotion and disease prevention programs and advancing public health science.

According to Service’s Web site, USPHS ranks correspond to ranks in the U.S. Navy, with LCDR equivalent to a major and CDR to a lieutenant colonel in the U.S. Army.

A slideshow of the ceremony is available [online](#).



LCDR Lindia Engram (Photo courtesy of Steve McCaw)



CDR Debra King (Photo courtesy of Steve McCaw)



LCDR John McLamb (Photo courtesy of Steve McCaw)

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NIEHS remembers Jenny Pronczuk de Garbino

By Eddy Ball

Friends and colleagues at NIEHS were saddened Sept. 20 by news of the death of global and children's health champion Jenny Pronczuk de Garbino, M.D., at age 63. Pronczuk de Garbino was a medical officer in the World Health Organization (WHO) Department of Public Health and Environment and, for a number of years, the co-principal investigator of a cooperative agreement between NIEHS and WHO. She collaborated with scientists at NIEHS on several initiatives to improve children's health and build effective partnerships worldwide.

One of Pronczuk de Garbino's closest friends at NIEHS was Bill Suk, Ph.D., director of the Center for Risk and Integrated Sciences. "Jenny was such a positive force for children's environmental health globally, a good friend and colleague not just to me but to so many people, and just about the nicest person I have ever known," he wrote after learning of Pronczuk de Garbino's death.

Pronczuk de Garbino was a clinical toxicologist and occupational health physician, originally from Montevideo, Uruguay, where she was appointed head professor of clinical toxicology and director of the National Poisons Centre. She trained at the Université de Paris, Lariboisière–St Louis in Paris and, through a Fulbright Scholarship, at Baylor College of Medicine.

Pronczuk de Garbino joined WHO in 1991 to work in the promotion of chemical safety (IPCS) and initiate work on the response to epidemics of toxic origin. Most recently, she worked on environmental threats and vulnerable population groups, specifically on the promotion of longitudinal cohort children's studies, international collaborative research, training of health care providers, and technical advice to governments worldwide.

In 2008, Pronczuk de Garbino was recognized by the US Environmental Protection Agency as the International Children's Environmental Health Champion. She will be remembered during the Council of Fellows at Ramazzini Days 2010.

In a message to friends and colleagues, WHO associate Marie-Noel Bruné said that condolences may be sent to a special email account, inmemoryofjenny@gmail.com, or to the family in Switzerland: Family Garbino – Pronczuk, Chemin de Ruisseau 4, 1297 Founex – Switzerland. Bruné also said that, in lieu of flowers or gifts, the family would appreciate donations to a children's environmental health initiative in Uruguay, Jenny's beloved home country.



Shown at a seminar at NIEHS in December 2008 ([see story](#)), Pronczuk de Garbino was known for her contagious laugh and her passion for making a difference in children's lives all over the world. (Photo courtesy of Steve McCaw)

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NICEATM convenes international workshop on vaccine safety testing

Submitted by Debbie McCarley

NIEHS scientists Rear Admiral William Stokes, D.V.M. and Dr. Warren Casey, Ph.D. joined other scientists from around the world last month at the “International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions.” Nearly 200 scientists from 13 different countries gathered to review the current state of the science and to recommend future research, development and validation efforts needed to advance alternative methods that can reduce, refine (lessen or eliminate pain and distress), and replace the use of animals for human and veterinary vaccine post-licensing potency and safety testing. The workshop, which took place Sept. 14-16 at NIH in Bethesda, Md., was organized by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) and the Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) in partnership with the European Centre for the Validation of Alternative Methods, the Japanese Center for the Validation of Alternative Methods, and Health Canada. The workshop was co-sponsored by the Society of Toxicology.

Vaccines are a vital and cost-effective public health tool in the prevention of a wide range of serious infectious diseases. In her remarks during the opening session of the workshop, Rear Admiral Anne Schuchat, M.D., director of the National Center for Immunization and Respiratory Diseases within the Centers for Disease Control and Prevention (CDC), noted the overwhelming impact of pediatric vaccines by stating, “For each birth cohort vaccinated with seven vaccines, direct health care costs are reduced by \$9.9 billion, 33,000 lives are saved, and 14 million cases of disease are prevented.” Similarly, James Roth, D.V.M., Ph.D., director of the Center for Food Security and Public Health at Iowa State University, emphasized in his presentation the importance of veterinary vaccines to both animal and human health. “Veterinary vaccines are essential for safe and effective food production, control of emerging and exotic diseases of animals and people, and reducing the transmission of foodborne diseases,” Dr. Roth noted.

Scientists from the U.S. Food and Drug Administration (FDA) and U.S. Department of Agriculture (USDA) joined scientists from Health Canada, the United Kingdom, Japan, and the World Health Organization in a panel discussion of ways to increase international harmonization of differing vaccine testing procedures.



In her keynote speech, Schuchat underscored the important role of safe and effective vaccinations in promoting public health. (Photo courtesy of William Stokes)



Stokes and Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) member Karen Brown, Ph.D., were among panelists at the workshop. (Photo courtesy of William Stokes)

Regulatory authorities require potency and safety testing of each vaccine production lot to ensure that it maintains the antigenic characteristics that make it effective and to prevent the release of vaccine lots that might cause serious adverse health effects. In his opening remarks, Stokes noted that while vaccines are vital for protecting human and animal health, the post-licensing testing required to ensure that each lot is safe and effective continues to require large numbers of animals for some vaccines. Annual research facility reports to the USDA also reveal that vaccine testing accounts for a significant number of animals experiencing unrelieved pain and distress. Accordingly, NICEATM and ICCVAM included vaccine testing as one of four highest priority areas in their [2008-2012 Five-Year Plan](#).

Workshop participants identified knowledge and data gaps that need to be addressed to develop methods that can further reduce, refine, and replace the use of animals in vaccine testing. Participants also identified and prioritized research, development, and validation activities needed to address these knowledge and data gaps, including the application of new science and technology to develop improved methods. They agreed that vaccines that use the largest number of animals, and that are associated with the greatest pain and distress, should be given the highest priority for development and validation of alternative test methods. Participants also emphasized the need to find ways to avoid or minimize testing with live viruses and bacteria that are hazardous to workers. Ways to promote the increased use of accepted methods were also discussed. Implementation of the workshop recommendations is expected to advance the availability and use of alternative methods for vaccine potency and safety testing, while ensuring continued protection of human and animal health.

The workshop provided a unique opportunity for stakeholders from the human and veterinary vaccine sectors to interact and gain important insights on similarities and differences in how potency and safety testing is currently conducted in each sector. Stokes, Casey, and 30 invited participants gave presentations, moderated sessions, and contributed to the breakout group discussions. Invited participants included scientists from the FDA, CDC, USDA, U.S. Department of Defense (DOD), National Institute of Allergy and Infectious Diseases (NIAID), as well as representatives from the governments of Japan, Canada, the United Kingdom, The Netherlands, and the European Union. National and multinational corporations and research institutions were also represented.



Several of the organizers posed for a group shot during a break in the workshop. In front, left to right, are Yoshinobu Horiuchi, Ph.D., Pharmaceuticals and Medical Devices Agency, Japan; Theresa Finn, Ph.D., FDA; Jodie Kulpa-Eddy, D.V.M., USDA; Stokes; and Richard McFarland, M.D., Ph.D., FDA. In the second row, left to right, are Juan Arciniega, D.Sc.; and Steven Rubin, Ph.D., FDA. In the third row, left to right, are Marlies Halder, V.M.D., Institute for Health and Consumer Protection; Robin Levis, Ph.D., FDA; Johan Descamps, Ph.D., GlaxoSmithKline, Belgium; Geetha Srinivas, D.V.M., Ph.D., USDA; and Jeffrey Galvin, Ph.D., Pfizer Animal Health. Shown in the fourth row, left to right, are Janet Skerry, U.S. Army Medical Research Institute of Infectious Diseases; Dorothea Sesardic, Ph.D., National Institute for Biological Standards and Control, U.K.; and Hajime Kojima, Ph.D., director, Japanese Center for the Validation of Alternative Methods. In the top row, left to right, are Paul Stickings, Ph.D., National Institute for Biological Standards and Control, U.K.; Ivo Claassen, Ph.D., Central Veterinary Institute, The Netherlands; Michael Schmitt, Ph.D., FDA; Richard Isbrucker, Ph.D., Health Canada; Casey; and Coenraad Hendriksen, D.V.M., Ph.D., Netherlands Vaccine Institute. (Photo courtesy of William Stokes)

NICEATM and the ICCVAM Biologics Working Group (BWG) were primarily responsible for organizing the workshop. The BWG is co-chaired by Jodie Kulpa-Eddy, D.V.M., of the USDA, and Richard McFarland, Ph.D., M.D., of the FDA. Dr. Kulpa-Eddy is also currently acting chair of ICCVAM. In addition to FDA and USDA, the BWG includes scientists from the CDC, DOD, U.S. Department of the Interior, NIEHS, and NIAID. Drs. Stokes and Casey are the NIEHS representatives on the BWG.

Presentations from the workshop will soon be available on the NICEATM-ICCVAM [Web site](#). Complete proceedings of the workshop, including manuscripts from speakers and breakout group sessions, will be published next year as a dedicated issue of *Procedia in Vaccinology*. An article summarizing the workshop discussions and conclusions will also be published in the journal *Biologicals*. The conclusions and recommendations resulting from the workshop will be provided to ICCVAM for prioritization of future research, development, and validation activities for alternative test methods that reduce, refine, and replace the use of animals in vaccine potency and safety testing.

(Debbie McCarley is the special assistant to Rear Admiral William Stokes, D.V.M., D.A.C.L.A.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.)

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NICEATM is organizing workshops on accepted alternative methods in 2011

A series of workshops to be organized by NICEATM on “Best Practices for Regulatory Safety Testing” will focus on methods currently accepted or endorsed by regulatory agencies that can reduce, refine, or replace animal use for common safety testing applications. The first two of these will be held early next year: “Assessing the Potential for Chemically Induced Eye Injuries” will take place on January 19, 2011, and “Assessing the Potential for Chemically Induced Allergic Contact Dermatitis (ACD)” will take place on January 20, 2011.

These one-day workshops will help participants gain a practical understanding of the theory and application of available methods that can be used to evaluate the hazard potential of chemicals and products, while minimizing animal use and avoiding pain and distress. Participants will learn the strengths and weaknesses of available alternative test methods, become familiar with the types of data they provide, and learn how to use these data in regulatory safety assessments. Scientists from industry, government, and academia that have an interest in learning more about the available alternative test methods for assessing potential eye injury or ACD hazards are encouraged to attend the workshops.

The workshops will be held on the campus of the National Institutes of Health in Bethesda, Md. Each workshop is free and open to the public with attendance limited only by the space available. Those interested may register for one or both workshops. Individuals who plan to attend are asked to register with NICEATM by January 6, 2011. Registration information, a tentative agenda for each workshop, and additional meeting information are available on the NICEATM-ICCVAM [Web site](#). Information is also available upon request from NICEATM (phone: 919-541-2384, email: niceatm@niehs.nih.gov).

The workshop series is being organized by NICEATM and ICCVAM, and is co-sponsored by the Society of Toxicology.

Institute celebrates postdoctoral fellows

By Eddy Ball

NIEHS reminded its 225 postdoctoral fellows of their central importance to the Institute's work by observing the second annual National Postdoc Appreciation Day Sept. 24 during the [NIEHS Trainees Assembly \(NTA\)](#) fall meeting. As attendees learned at the meeting, the national celebration gained added momentum the day before with a Congressional resolution honoring America's postdoctoral fellows and "the significant contributions that postdoctoral scholars make to the U.S. scientific research enterprise."

National Postdoc Appreciation Day is the high point of National Postdoc Appreciation Week. The celebration was initiated in 2009 by the [National Postdoctoral Association](#), a member-driven organization that provides a unique voice for postdoctoral scholars throughout the country.

On hand to offer their personal thanks to the Institute's postdocs were NIEHS/NTP Director Linda Birnbaum, Ph.D., and NIEHS Acting Scientific Director David Miller, Ph.D. Birnbaum entertained postdocs with stories of her own three fellowships — one of them at NIEHS. She encouraged her listeners to "take advantage of opportunities [at NIEHS] to broaden yourself professionally," and said, "You should always be appreciated."

Miller offered "an extended thank you to all our trainees" and to Diane Klotz, Ph.D., director of the [NIEHS Office of Fellows Career Development](#). He said, "I think of science as an engine and the fuel for the engine is the trainees." Miller also emphasized that principal investigators benefit from the fresh ideas and enthusiasm of postdocs in ways that trainees and their supervisors may not fully appreciate.

NTA steering committee chair Nisha Cavanaugh, Ph.D., spoke during the meeting portion of the event, updating fellows on volunteer opportunities and new initiatives, as well as recent and upcoming events. She pointed to the NTA selection of Mentor of the Year for NIEHS Science Day Nov. 4 and the new emphasis on landing a job at the upcoming 14th Annual Biomedical Career Fair scheduled for April 29, 2011.

Closing out the business portion of the meeting, Klotz added her own humorous touch to the meeting by describing her career path, which was similar to the one many fellows may experience — one that took her in unexpected directions as she eventually discovered her own kind of rewarding career in science.



Birnbaum assured NIEHS postdocs that many fruitful career paths, like her own, have hesitations and shifts before getting on the right trajectory. (Photo courtesy of Steve McCaw)



Miller took over as acting scientific director Sept. 20. Like his predecessor and longtime friend and colleague, John Pritchard, Ph.D., he has a deep appreciation for the talent and dedication of postdocs at the Institute. (Photo courtesy of Steve McCaw)

Klotz described upcoming training and career development events and the creation of a special listserv to support the NTA's new Visiting Fellows Subcommittee. Chaired by Louie Chen, Ph.D., and Raj Gosavi, Ph.D., the committee will strive to help the 110 fellows from foreign countries with some of their specialized needs.

When the meeting came to an end, fellows gathered for a group photo and then filed into the NIEHS cafeteria for an ice cream social and trivia contest.



After speaking at the NTA meeting, Klotz came once more to the podium — this time in the cafeteria during the trivia competition. (Photo courtesy of Steve McCaw)



Cavanaugh facilitated the business portion of the meeting, with help from postdocs Allison Schorzman, Ph.D., who reported on the first NTA picnic, and Thaddeus Schug, Ph.D., who talked about his experiences as guest writer for the Environmental Factor. (Photo courtesy of Steve McCaw)



Pictured above, Senior Principal Investigator Mitch Eddy, Ph.D., showed just how much the crowd enjoyed the trivia contest. (Photo courtesy of Steve McCaw)



Shown, left to right, NTA Steering Committee members Jill Hesse, Ph.D., and Allison Schorzman, Ph.D., joined Principal Investigator Ken Tomer, Ph.D., Miller; and Birnbaum for talk and laughter at the event. (Photo courtesy of Steve McCaw)



Postdocs gather for the official 2010 Postdoc Appreciation Day group photo, which will be displayed at NIH in Bethesda, as well as here at NIEHS. (Photo courtesy of Steve McCaw)

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Science Notebook

The involvement of Mullerian Inhibiting Substance in ovarian cancer

By Robin Arnette

According to Harvard Professor Patricia K. Donahoe, M.D., Mullerian Inhibiting Substance (MIS), a protein involved in human sex determination, can play an important role in the treatment of a progenitor-like subset of cells in human ovarian cancer. This research may lead to patient specific treatment strategies and could produce novel therapies for ovarian cancer, an illness with few treatment options.

Donahoe discussed the work during the first lecture of the 2010–2011 NIEHS Distinguished Lecture Series on September 14. As the first woman to receive a full professorship in the department of surgery at Harvard Medical School, Donahoe began her talk by explaining how she started studying cancer.

“MIS from the testes in a developing male embryo causes the Mullerian duct to completely regress,” she said. “It occurred to us early in the course of these studies that if there was a substance that caused complete regression of a fetal duct, it would be interesting to find out whether it had an effect on tumors emanating from that same embryonic source.” The Mullerian duct gives rise to the Fallopian tubes, uterus, cervix, and upper portion of the vagina in the female.

She went on to say that since she and others made that connection in the 1970s, scientists have determined that many of the pathways important in embryonic development are also expressed in human cancers. One of the first people to see a link was Bob Scully, M.D., a Massachusetts General Hospital cancer pathologist who found that ovarian cancer, clinically known as a serous cystadenocarcinoma, resembled the Fallopian tube.

Donahoe explained that MIS is a member of the TGFbeta family. When she and her group tested MIS — made in the laboratory by David MacLaughlin, Ph.D. — against a number of mouse Mullerian duct tumors called MOVCARs and human ovarian cancer cell lines, they saw regression of the tumors. Donahoe originally



Donahoe is the Marshall K. Bartlett Professor of Surgery and Director of the Pediatric Surgical Research Laboratories at the Harvard Medical School Massachusetts General Hospital. (Photo courtesy of Steve McCaw)



Korach praised Donahoe's exemplary career by saying, "She took a clinical observation and made it a basic science question and found the gene, receptor, and the signaling pathway. That is how an investigator makes a major impact [on a field]." (Photo courtesy of Steve McCaw)

worked with a pharmaceutical company to clone MIS and produce recombinant MIS; she is now attempting to establish a partnership with industry to produce sufficient MIS for clinical trials. This larger quantity of MIS will allow her team to shed more light on the molecular mechanisms by which MIS causes the inhibition of growth of ovarian cancers.

“We know that MIS downstream signaling occurs through the SMAD1, 5, and 8, and that subsequent release of FKBP12, affects multiple pathways that will determine how the drug works downstream.”

Donahoe’s goal is to be able to separate the cells from an ovarian tumor into two populations: stem cell enriched and non-stem cell. After completing that step, she’d like to test the responsiveness of both cell groups to chemotherapeutic agents and biologics such as MIS. “We can then determine expression profile differences and begin to understand the molecular basis for asymmetric cell division, which is one of the great unsolved biological mysteries,” she added.

Kenneth Korach, Ph.D., Chief of the Laboratory of Reproductive & Developmental Toxicology, served as host for Donahoe’s seminar.

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Laboratory of Reproductive and Developmental Toxicology investigator Mitch Eddy, Ph.D., and Deputy Scientific Director William Schrader, Ph.D., listened intently to the lecture. (Photo courtesy of Steve McCaw)



National Toxicology Program Staff Scientist Retha Newbold and Toxicology Branch Geneticist Jack Bishop, Ph.D., were part of the heavily attended seminar. (Photo courtesy of Steve McCaw)

New BPA research helps fill research gaps

By Robin Mackar

Barely a year after NIEHS announced \$30 million in funding to support research on the chemical bisphenol A, new grantee findings are already emerging. [Gail Prins, Ph.D.](#), of the University of Illinois at Chicago, presented data during a seminar at NIEHS on how the dose levels and the route of administration of BPA given in her rat model are relevant to human exposure levels.

The lecture, organized by Jerry Heindel, Ph.D., an acting branch chief in the NIEHS Division of Extramural Research and Training, attracted an at-capacity audience Sept. 21. It began with an introduction to the rat model Prins uses for her work and an overview of prostate cancer — the second leading cause of cancer death in American men behind lung cancer.

Linking exposures to development of prostate cancer

To give the audience a better appreciation of her lab’s neonatal rat model and how it is helping to understand the developmental origins of diseases like prostate cancer in humans, she paralleled the progressions of the disease,

including how it slowly gets to a point referred to as prostate intraepithelial neoplasia (PIN), before breaking through a membrane and becoming full-blown prostate cancer.

As someone who has been studying the developmental basis of adult disease for several decades, Prins said she wanted to determine if the risk of prostate cancer could be determined by maternal or perinatal factors. Prins used a rat model, noting that prostate development in the rat originates at 19 days gestation, providing an ideal model for modulating a hormonal environment. Her lab demonstrated that right before birth and up to ten days afterwards is a critical reprogramming window for toxicants with regard to the prostate gland.

Prins said her lab developed what she referred to as a two-hit model, giving rats low doses of estrogenic compounds including BPA, soon after birth, and then testosterone and estradiol later in life, to mimic what happens with aging in humans. Using this model, she has shown that low doses of estrogen and BPA early in life would impact the susceptibility of prostate cancer later in life.

Closing the gap between human and animal studies

“The National Toxicology Program, in its 2008 evaluation of BPA, and the scientific community identified a very relevant and important research gap area that needed to be addressed,” said Prins. Reviewers wanted to know if the doses given to animals were similar to what humans experience ([see text box](#)).

They also said that the oral route of exposure was preferred because other routes of exposure produced higher levels of free/active BP. Prins said she now has the data to answer both research gaps — “Knowing the internal dose of BPA, rather than the dose administered to the animal, and how the organs respond to that dose, is the biologically relevant piece of information that was missing.”

She said studies published by her group demonstrated that early life exposure to environmentally relevant doses of BPA increases susceptibility to prostate carcinogenesis in animal models. She ended her talk by saying she believes these animal findings are applicable to humans.

Prins’ new data is scheduled for publication online this month in *Reproductive Toxicology*.

(Robin Mackar is the News Director in the NIEHS Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)



Prins, standing, shared some lab humor with NIEHS Deputy Scientific Director Bill Schrader, Ph.D., who asked about details of her experiments with rats and human cells. (Photo courtesy of Steve McCaw)



Space was at a premium for this popular talk scheduled only a few days earlier. (Photo courtesy of Steve McCaw)

Determining relevant levels of BPA

In her experiments, Prins showed that a subcutaneous injection of BPA at 10 micrograms per kilogram of body weight resulted in a serum level free/active BPA of 1.77 nanograms per milliliter after 30 minutes, which is in the range of human blood levels of free/active BPA. Thus, her dosing paradigm produced BPA levels that were relevant to human exposures.

Prins and her colleagues then designed a study to directly compare different routes of exposure of BPA, including subcutaneous and oral dosing, in a neonatal rat model. Her team then looked at how the delivery of 10 micrograms BPA per kilogram of body weight impacted the susceptibility of prostate cancer in the newborn rats exposed to BPA. The results showed that while the subcutaneous dosing did indeed show a seven-fold increased exposure in the first 30 minutes, by two hours the level of free/active BPA in the blood was similar for both dosing paradigms. Most importantly, both routes of exposure resulted in the same increased PIN level in the prostate, indicative of a precancerous toxicity seven months after the exposure. She noted that this data shows that route of exposure is not as critical as had been thought and thus the subcutaneous exposure route should be an acceptable paradigm.

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JBC selects NIEHS study as paper of the week

By Jeffrey Stumpf

A recent report from researchers in the NIEHS [Mitochondrial DNA Replication Group](#) was chosen as The Journal of Biological Chemistry (JBC) Paper of the Week — an honor awarded to the top one percent of reviewed manuscripts for their significance and overall importance.

Published Sept. 24, the [study](#) coauthored by Matthew Longley, Ph.D., Margaret Humble, Farida Sharief, and William Copeland, Ph.D., describes novel purification methods for the mitochondrial helicase encoded by the human *C10orf2* gene. The research team also characterized partial biochemical defects in twenty mutant variants identified in patients with mitochondrial disease.

The mitochondrial helicase is involved in mitochondrial genome (mtDNA) maintenance. Mutations in *C10orf2* co-segregate with people afflicted with heritable fatal mitochondrial diseases, such as the adult-onset Progressive External Ophthalmoplegia, hepatocerebral mtDNA depletion syndrome, and infantile-onset spinocerebellar ataxia. These mitochondrial diseases are characterized by mtDNA depletion and deletions leading to decreases in energy production in tissues.



Staff Scientist Matthew Longley, above, is first author of the team's JBC Paper of the Week. According to the journal's editors, "About 50 to 100 papers are selected from the more than 6,600 we publish each year." (Photo courtesy of Steve McCaw)

Biochemical defects discovered in helicase disease variants

Helicases are enzymes responsible for unwinding the two DNA strands at the DNA replication fork, which is necessary for mtDNA stability. However, the extent that mtDNA instability causes mitochondrial diseases is unknown, partly because the mechanism for replicating mtDNA remains unclear.

Longley said he believes that a biochemical approach begins to address these uncertainties. “The accurate determination of biochemical dysfunction is critical to identifying molecular mechanisms underlying disease.”

The study describes four basic measurements of the mitochondrial helicase required for its function:

- Binding to single-stranded and double-stranded DNA as measured by fluorescence anisotropy, a method that detects the change in the speed of rotation of DNA when a large molecule is bound
- ATPase activity, which is required for helicase function
- Protein stability as estimated by the rate of inactivation of ATPase activity at temperatures that induce unfolding of less stable proteins
- The ability to unwind double-stranded DNA

All of the mutant variants exhibited variable helicase activity, suggesting, as Copeland explains, that changes in helicase function contribute to mtDNA instability. “We believe these subtle changes are consistent with the late presentation of disease in most of these patients.”

Determination of optimal purification conditions

Protein instability and aggregation, which have hampered previous analyses of this enzyme by other labs, complicated purification of the mitochondrial helicase. Longley and colleagues described purification schemes for the His-tagged and untagged mitochondrial helicase that had been overproduced in *E. coli* cells, utilizing combinations of immobilized metal affinity, anion exchange, and heparin affinity chromatography. The protein precipitated without careful consideration of the buffer components. Precipitation was minimized by increasing the concentrations of both salt and glycerol, as well as by the addition of detergents and magnesium ions.

The survey of optimal purification conditions helped to determine appropriate conditions for enzymatic assays *in vitro*. Others have reported a lack of helicase activity for certain purified mitochondrial helicase disease variants. However, Longley explains that these discrepancies demonstrate the differences in optimal and suboptimal experimental conditions. “This work emphasizes the importance of maintaining enzyme stability and assessing enzymatic activities under carefully optimized conditions.”



NIEHS Biologist Margaret Humble is second author on the study. (Photo courtesy of Steve McCaw)



Prior to her recent retirement, Sharief, above, was a biologist in the group. (Photo courtesy of William Copeland)

Future biochemical work could help to determine why a single mutant copy of the *C10orf2* gene causes disease. The native helicase is a complex of six identical subunits. Mixtures of wild type and mutant proteins in affected patients could form so-called “heterohexameric” helicases with enzymatic functions altered in complex ways. Alternatively, reduced abundance of the wildtype helicase may be sufficient to cause mtDNA instability. The optimal biochemical conditions worked out in this study will be instrumental in defining the dominant-negative biochemical effect expected to underlie the dominant nature of these diseases.

Citation: Longley MJ, Humble MM, Sharief FS, Copeland WC. 2010. Disease variants of the human mitochondrial DNA helicase encoded by C10orf2 differentially alter protein stability, nucleotide hydrolysis and helicase activity. J Biol Chem. DOI: 10.1074/jbc.M110.151795.

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group.)

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Principal Investigator William Copeland is head of the NIEHS Mitochondrial DNA Replication Group. (Photo courtesy of Steve McCaw)

Council hears two science talks at fall meeting

By Eddy Ball

At the meeting of the National Advisory Environmental Health Sciences Council Sept. 1-2 ([see related story](#)), NIEHS once more honored the tradition of showcasing its science and giving members a welcome respite from the program reports. For its fall meeting, members enjoyed presentations by grantee Sven-Eric Jordt, Ph.D., and by NIEHS Principal Investigator Mike Resnick, Ph.D.

In 2006, [Jordt](#) was selected as one of the first NIEHS Outstanding New Environment Scientist (ONES) awardees and is the principal investigator of a grant under the NIH CounterACT program administered by NIEHS. The next year, Jordt became the first NIEHS grantee to be honored with a Presidential Early Career Award for Scientists and Engineers (PECASE).

[Resnick](#) is head of the NIEHS Chromosome Stability Group and a veteran investigator with a long list of honors and outstanding publications (see this month’s [summary](#) of his most recent Paper of the Month). Resnick was honored as NIEHS Scientist of the Year in 2008, and since the inception of the “Best Paper of the Year” at NIEHS in 2003, his group has received this award for 2003, 2004, and 2007.



Jordt said of his work over the past four years, “It definitely wouldn’t have been possible without generous funding by NIEHS.” (Photo courtesy of Steve McCaw)

Jordt and Resnick are examples of NIEHS-funded investigators involved in basic research, with promising translational potential for treating and preventing human injury and disease.

TRP channels in chemical sensing and environmental disease

Jordt's work has its roots in his postdoctoral research on the mechanisms of transient receptor potential (TRP) channel receptors, which are part of an early warning system of sensory neurons activated during injury and chronic painful conditions. These receptors trigger tears, sneezing, neurogenic inflammation, pain, and respiratory constriction in the upper airway.

A series of important papers by Jordt's group over the past four years has uncovered the role of TRP channel activation, specifically TRPA1, in mammalian responses to noxious chemical and physical stimuli, such as cigarette smoke, tear gas agents, and chlorine. Recent work by the group has expanded investigations into the role of sensory neuronal ion channel activation in producing airway inflammation and hyperactivity in allergic asthma ([see related story](#)).

In his work with wildtype and TRPA1 knockout mice challenged with ovalbumin, Jordt and his colleagues have experimented with a TRPA1 antagonist, HC-030031, that was found to be protective in exposure to noxious gases. The antagonist, they found, also gave wildtype mice the same protection as that enjoyed by the genetically modified mice against the asthmatic response, inhibiting eosinophil infiltration and preventing the development of airway hyperreactivity.

Jordt's recent work also addresses the TRPM8 cold-sensitive channel activated by menthol and may support efforts by public health advocates to end use of this anti-inflammatory agent in cigarettes.

The expanding universe of p53 targets

As the latest step in his basic research on genome stability, Resnick entered into an innovative Intramural Research Award collaboration last year ([see related story](#)) with two NIEHS clinical investigators, Michael Fessler, M.D., and Stavros Garantziotis, M.D.

In his Council presentation, Resnick reviewed his group's findings from research on budding yeast and human cells and the work that informs the new paper that Resnick, Fessler, and Garantziotis, along with Chromosome Stability Group members Daniel Menendez, Ph.D., and Maria Shatz, Ph.D., have recently submitted for publication — "The human Toll-like receptor (TLR) family is integrated into the DNA damage and p53 response network."

Resnick reviewed the tumor suppressor p53 as the "guardian of the genome" in its role as a sequence-specific transcription factor and master regulator of more than 200 genes and non-coding sequences in the human genome, and he described recent findings that greatly expand the p53 network of target genes. With his cross-disciplinary collaborations, Resnick is investigating the evolution of p53 networks, including ones that seem to be primate specific, and addressing what he calls "the dramatic synergy" of the estrogen receptor and p53 networks.



Before telling the audience about the technical details of his work, Resnick summarized his group's research interests in everyday language. "We think about the genome, whether it's stable or not, and what are the consequences of throwing stuff at it, whether it's internal stuff or external stuff." (Photo courtesy of Steve McCaw)

Studies of human primary lymphocytes from healthy volunteers have revealed p53 control of most human TLR genes and shed light on the mechanisms of p53 control and its involvement in variations in innate immunity. These findings will likely have potential implications in terms of better understanding individual susceptibility to environmentally linked diseases and for the advancement of personalized medicine.

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Evaluating the science on cell phone safety

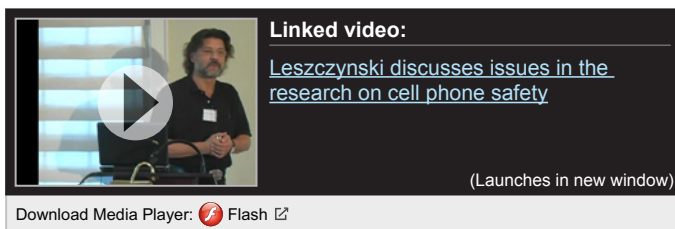
By Mamta Behl

As part of its ongoing efforts to evaluate the toxicity and carcinogenicity of cell phone radiofrequency radiation, the National Toxicology Program (NTP) invited world-renowned researcher, Dariusz Leszczynski, Ph.D., D.Sc., to share his views on the status of current science regarding cell phone safety, as well as the need for more and better designed studies. Also speaking at the Aug. 30 seminar was NTP toxicologist Michael Wyde, Ph.D., project leader for cell phone radiation studies currently underway in a specially designed facility in Chicago.

Leszczynski is a professor at Säteilyturvakeskus (STUK) and the Radiation and Nuclear Safety Authority in Helsinki, Finland. Leszczynski also held until recently the position of Guangbiao Professor at the Zhejiang University School of Medicine in Hangzhou, China. He is an adjunct professor of biochemistry at the University of Helsinki.



Leszczynski is actively involved in various task groups and steering committees associated with cell phone studies. He has also been invited by the World Health Organization and U.S. Food and Drug Administration to review research agendas related to mobile phone safety. (Photo courtesy of Steve McCaw)



According to the [International Telecommunication Union](#), an estimated 4.6 billion cell phones are in use worldwide, with some 270 million units operating in the U.S. alone. Concerns about the health effects from widespread exposure to radiofrequency radiation have led to a proliferation of studies but, according to Leszczynski, investigators haven't always been asking the right questions. "It is a common misconception that thousands of papers are published, but [in fact] most of them do not evaluate cell phone radiation," he said.

Leszczynski emphasized that studies have mostly focused on cancer while ignoring other important non-cancer endpoints such as



Wyde's presentation reflected the careful design of the NTP study, which addresses the shortcomings that Leszczynski had pointed out in his review of animal studies. (Photo courtesy of Steve McCaw)

general toxicity, stress response, blood brain barrier permeability, and effects on vital organs other than brain. In discussing limitations of epidemiological studies, which often utilize blood pressure, headaches, allergic responses, and electroencephalograms (EEGs) to study radiation effects, Leszczynski cautioned that results may be skewed by the experimental design and evaluation of inappropriate endpoints and non-objective responses of study subjects.

At this time, he maintained, “we do not know if humans respond to mobile phone radiation.” In his opinion, more epidemiological studies like the [Cohort Study of Mobile Communications \(COSMOS\)](#), the largest European-based research effort on mobile phone safety, are needed to evaluate exposure to cell phone radiation in humans. He also stressed the need for studying molecular level responses to mobile phone radiation in humans, in order to determine whether the human body is indeed affected by this radiation.

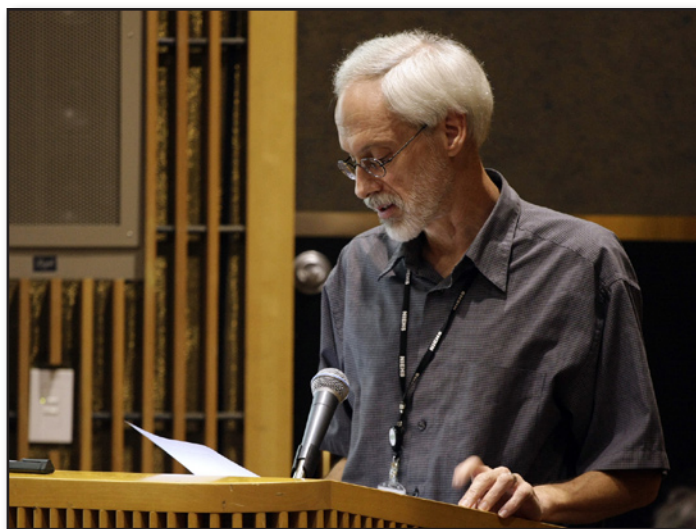
“Currently we don’t have any studies on children [and] we don’t know if they are more sensitive,” Leszczynski added. He concluded by emphasizing the need for more targeted research since “current literature does not provide sufficient evidence for safety standards in protecting mobile phone users.” He identified the importance of developing more realistic dosimetry models and strongly advocated the use of alternative methods such as omics technologies to investigate genes and proteins which may potentially be altered as a result of exposure to cell phone radiation.

In the meantime, Leszczynski advises, “Use caution, especially for children with phones, and limit exposure to mobile phones when possible.”

Following Leszczynski’s talk, Wyde presented an update on the current status of the NTP studies in rats and mice on the exposure to cell phone radiofrequency and radiation. The studies will address several limitations in the literature and will make an important contribution to the better understanding of cell phone safety. Selection of radiofrequency in these studies is based on human exposure and lies in the non-thermal range. The studies are designed to assess carcinogenic and non-carcinogenic endpoints including general toxicity, blood-brain barrier permeability, and molecular alterations. They are expected to be completed by 2013.

(Mamta Behl, Ph.D., is a research fellow in the NTP Toxicology Branch.)

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NTP Associate Director John Bucher, Ph.D., was host of the two-hour seminar. (Photo courtesy of Steve McCaw)



NIEHS Principal Investigator and Director of the Microarrays Core facility Rick Paules, Ph.D., was one of several attendees who joined NTP scientists at the presentation. (Photo courtesy of Steve McCaw)

BPA researchers and regulators meet for update and integration

By Thaddeus Schug

NIEHS grantees and government scientists gathered Sept. 21-22 at NIEHS to update their research efforts on bisphenol A (BPA). The purpose of the meeting was to share new findings and coordinate their research efforts to develop a comprehensive assessment of possible human health effects due to BPA exposure.

BPA is a chemical used to produce polycarbonate plastics and epoxy resins that coat the linings of canned food and drink containers. It is also reported to be in high concentrations on certain retail receipt papers and baby bottles. Humans are exposed to BPA when the chemical leaches from these products. BPA exposure has been linked to a variety of physiological problems in animal studies such as infertility, weight gain, behavioral changes, early onset puberty, prostate and mammary gland cancer, and diabetes.

NIEHS/NTP Director Linda Birnbaum, Ph.D., opened the meeting saying, “We know that many people are concerned about bisphenol A, and we want to support the best science we can to provide the answers. Clearly, there is significant evidence from animal studies showing that BPA exposure is a health concern, but there are large data gaps on the health effects of this chemical that must be addressed to fully determine its impact on human health.”

Jerry Heindel, Ph.D., the meeting organizer and acting branch chief at NIEHS who oversees much of the Institute’s portfolio on BPA, said, “Having BPA researchers and officials from regulating agencies such as the U.S. Food and Drug Administration (FDA) and the European Food Safety Authority (EFSA) together encourages interactions and the development of reliable and reproducible methods that will allow us to determine the potential threat that exposure to BPA poses to public health.”

Heindel added, “The goal of the meeting is for researchers — grantees and scientists from NIEHS, the National Toxicology Program (NTP), and FDA — to share their current data, identify additional collaborations and data-sharing possibilities, and address areas of inadequacy and inconsistency in the data.”

NIEHS has invested heavily in research related to BPA and other endocrine disrupting chemicals. In 2009, NIEHS awarded 11 BPA Grand Opportunities and Challenge grants, and currently funds a total of 35 projects studying the health effects and risks associated with BPA exposure. The NTP is also collaborating with FDA’s



Birnbaum, left, NTP Associate Director John Bucher, Ph.D., center, and NTP Center for the Evaluation of Risks to Human Reproduction Director Kristina Thayer, Ph.D., were active participants in the meeting. (Photo courtesy of Steve McCaw)



Recent Heinz awardee, Frederick vom Saal, right, leads a panel discussing BPA dose measurements and pharmacokinetics. He was joined by Wade Welshons, Ph.D., of the University of Missouri-Columbia, center, and NCTR pharmacologist Jeffrey Fisher, Ph.D., left. (Photo courtesy of Steve McCaw)

National Center for Toxicological Research to examine long-term health outcomes resulting from developmental exposures.

“We are excited and thankful for the willingness of NIEHS and NTP researchers to share and exchange knowledge to expand our understanding of the health risks associated with BPA exposure, said Jordi Serratos, Ph.D., EFSA liaison officer at FDA.

During day one of the meeting, participants shared data on how BPA is absorbed, distributed, and processed in animal models and humans. Much discussion centered on new findings that indicate rodents are similar to primates in the way they metabolize and clear BPA from their bodies. “We no longer need to waste valuable resources and time on establishing the adequacy of our testing models,” said Frederick vom Saal, Ph.D., a longtime BPA researcher from the University of Missouri. “We can now focus our attention on determining the toxicity of this chemical.”

In addition to general sessions, the meeting included breakout groups. Animal and human BPA researchers gathered to discuss their human and animal research collaborations and data needs. Epidemiologists and animal researchers studying the same disease endpoints addressed how to stimulate translation of research between groups.

“I think what this [meeting] has proven is that there is much more that we don’t know than we do know about the health effects due to BPA exposure,” said Jodi Flaws, Ph.D., of the University of Illinois, who directed a large group discussing reproductive issues. “We need to continue to communicate and share endpoints between our animal and human studies.”

The meeting ended with an update of the NTP/FDA 90 day study of BPA exposure in rodents from the FDA National Center for Toxicological Research pharmacologist Barry Delcos, Ph.D., which is nearing the midpoint of testing.

(Thaddeus Schug, Ph.D., is a postdoctoral research fellow in the NIEHS Laboratory of Signal Transduction and a regular contributor to the Environmental Factor. He is currently on detail as a program analyst in the NIEHS Division of Extramural Research and Training.)

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Researchers filled Rodbell Auditorium to share findings and listen to updates on BPA research. (Photo courtesy of Steve McCaw)



NIEHS Outstanding New Environmental Scientist (ONES) grantee, Heather Patisaul, Ph.D., takes notes during the meeting. Patisaul leads a project aimed at determining the impact of BPA exposure on brain development. (Photo courtesy of Steve McCaw)



ONES grantee, Dana Dolinoy, Ph.D., far left, and NTP Staff Scientist Retha Newbold, far right, look on as Heindel leads one of the many discussion sessions. Heindel said, “We need more collaboration and integration of data between groups and across species in order to move this field along.” (Photo courtesy of Steve McCaw)

Regulation of cellular genotoxic response

By Ritu Rana

Cell biologist Yoshiaki Tsuji, Ph.D., shared his new findings on the ways genotoxic stresses perturb cellular signaling pathways, contribute to toxicity, and influence disease outcomes in a talk Sept. 7 at NIEHS. His discussion of the transcriptional regulation of antioxidant genes by homeodomain-interacting protein kinase 2 (HIPK2) was the latest presentation in the monthly Receptor Mechanisms Discussion Group seminar series.

Tsuji is an associate professor in the Department of Environmental and Molecular Toxicology at North Carolina State University. His laboratory's main research interest is understanding how oxidative stress affects genomic integrity and iron homeostasis of cells and how this stress is implicated in neurodegenerative diseases. In addition to funding from NIH research project and supplement grants, Tsuji's work supports the research projects of several trainees in the NIEHS [training grant](#) managed by Health Scientist Administrator Carol Shreffler, Ph.D.

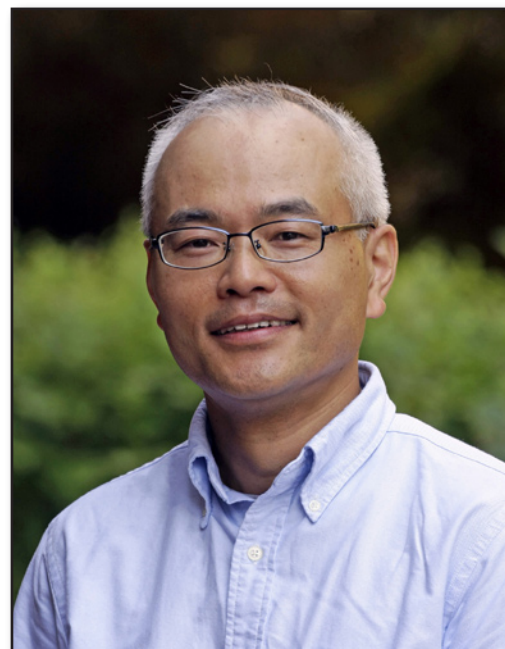
As Tsuji explained, iron plays an essential role in many cellular functions, but excess iron is potentially harmful because it can catalyze the formation of reactive oxygen species (ROS). Elucidating the role of HIPK2 in the regulation of iron storage proteins may provide insight into possible strategies for modulating the effects of oxidative stress.

Roles and regulation of genes encoding key proteins in iron metabolism

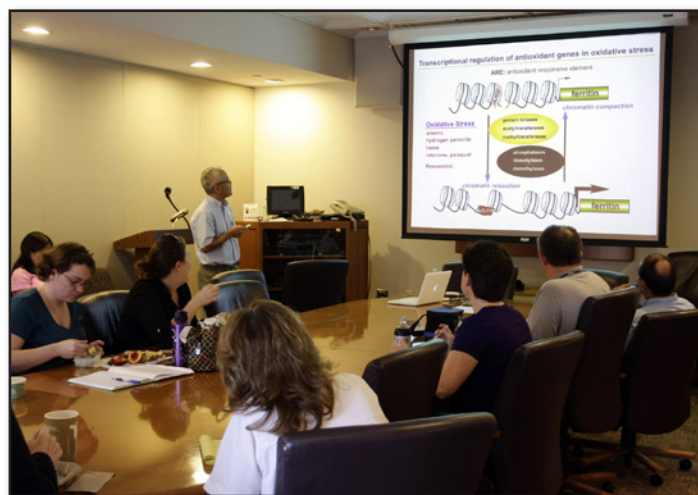
In his talk, Tsuji discussed the newly identified role of HIPK2 in differential phosphorylation of transcription factors, such as activating transcription factor 1 (ATF-1) and cAMP response element binding (CREB), in response to genotoxic stress. The first part of the talk was focused on gene regulation of an iron storage protein, ferritin.

According to Tsuji, ferritin H is activated in response to oxidative stress through its antioxidant response element (ARE) and is thought to have a potential role as an antioxidant in iron-catalyzed oxidative damage. ATF-1 binds ARE sites in the ferritin H enhancer region and represses gene expression.

HIPK2, as an ATF-1 binding protein, phosphorylates ATF-1 at a novel serine residue and modulates ATF-1-mediated repression of the human Ferritin H gene. Thus, HIPK2 indirectly regulates ferritin-H gene expression and imparts cytoprotection to the cells under oxidative stress.



Guest lecturer Yoshiaki Tsuji heads a group at N.C. State University that explores molecular mechanisms by which cellular susceptibility to cytotoxic agents and stresses are determined in normal and cancer cells. (Photo courtesy of Steve McCaw)



Principal investigators and fellows gather each month for the lunchtime presentations in the NIEHS Executive Conference Room. (Photo courtesy of Steve McCaw)

Maintaining viability and generation of neuronal cells

The second half of the talk included Tsuji's work on the HIPK2-mediated regulation of another important transcription factor, CREB, which plays a critical role in cell survival and adaptive responses. He further elaborated the mechanism, describing how the phosphorylation of CREB by HIPK2 at a novel site facilitates the recruitment of coactivator proteins such as CREB-binding protein (CBP) and activates the gene function.

Tsuji also showed that HIPK2 regulates the gene expression of brain-derived neurotrophic factor (BDNF) under genotoxic stress. Hence, HIPK2 has an important role in supporting neuronal cell viability and proliferation under conditions of oxidative stress.

Laboratory of Reproductive and Developmental Toxicology Chief Kenneth Korach, Ph.D., hosted Tsuji at the Receptor Mechanism Discussion Group. This monthly research seminar series provides an excellent opportunity for invited scientists to present and discuss their research work with the NIEHS scientific community.

(Ritu Rana, Ph.D., is a visiting fellow in the NIEHS Human Metabolism Group in the Laboratory of Toxicology and Pharmacology.)

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New opportunities in autism research

By Ed Kang

Researchers and advocates came together Sept. 8 to offer new strategies and opportunities for progress in autism research. The meeting, titled "Autism and the Environment: New Ideas for Advancing the Science," was held at NIEHS' Keystone building and sought to bring the lessons learned from other fields to bear on the unique challenges of autism spectrum disorders (ASD).

Scientists and patient and parent advocates from within the field of autism had a rare opportunity to brainstorm with those experienced in other disorders with environmental risk factors, including Parkinson's disease and breast cancer. Ultimately, the recommendations of the panel will inform future research initiatives and activities ([see text box](#)).

"The impetus for the meeting is the recognition that a more concerted and strategic effort is needed to accelerate progress in understanding environmental contributors to autism, so we can both prevent and intervene," said Linda Birnbaum, Ph.D., director of NIEHS and the National Toxicology Program. "Our goal is to identify novel opportunities and mechanisms to accelerate research guided by the recent advances in autism, emerging tools and technologies in environmental health sciences, and analogies to successful approaches used in other environmentally mediated diseases."



Issac Pessah, Ph.D., veteran grantee from the University of California, Davis, is joined by Cindy Lawler, Ph.D., health scientist administrator in the Cellular, Organ and Systems Pathobiology Branch in the NIEHS Division of Extramural Research and Training. In leading the discussion, Lawler stressed the value of diverse backgrounds and viewpoints in light of a complex disease that is "not one autism, but many autisms." (Photo courtesy of Steve McCaw)

The session was co-sponsored by [Autism Speaks](#), a non-profit group that raises awareness of ASD and sponsors autism-related research.

As a starting point for future activities, a report of the meeting's discussion points will be shared with the NIH Interagency Autism Coordinating Committee and the public, through the NIEHS and Autism Speaks Web sites.

A complete list of meeting participants is available [online](#).

(Ed Kang is a public affairs specialist in the Office of Communications and Public Liaison and a regular contributor to the Environmental Factor.)

Looking ahead in autism research

Charged with identifying the best opportunities for accelerating research to better understand the role environment plays in autism, the group offered many possibilities:

- Hypothesis-driven science in parallel with discovery science.
- Interdisciplinary research that encourages interaction of epidemiologists and clinicians with basic scientists.
- Prospective epidemiological approaches using personal sensors and other available/emerging tools to collect detailed information about environmental exposures.
- Exploration of higher prevalence in suspected 'clusters' or pockets and the examination of underlying exposures.
- Study of gender differences — males being 4 times more likely than females to suffer from ASD — and gender-specific vulnerabilities to toxicants and other exposures, particularly prenatally.
- Use of existing large data sets, including biological samples, to encompass genetic, environmental and phenotype information.
- Increased use of bioinformatics and biostatistical analysis.
- Incorporation of immunotoxicological approaches.
- Development of refined animal models and induced pluripotent stem cells.
- Understanding linkages between autism and medical conditions such as gastrointestinal and immune response disorders.



Experts from various fields contribute to the autism discussion. Pictured left to right are Ray Tice, Ph.D., chief of the NTP Biomolecular Screening Branch; Tom Knudsen, Ph.D., a biologist at the U.S. Environmental Protection Agency's National Center for Computational Toxicology; and Lisa Boulanger, Ph.D., assistant professor of molecular biology at Princeton. (Photo courtesy of Steve McCaw)



Geraldine Dawson, Ph.D., chief science officer for Autism Speaks, called autism a “public health crisis.” She said, “Autism was considered a rare condition, and now we see it is the most prevalent neurodevelopmental disorder today — a 600 percent increase in the last two decades.” This year, more children will be diagnosed with autism than diabetes, childhood cancer and cystic fibrosis combined. (Photo courtesy of Steve McCaw)



Panelists ponder epidemiological approaches in autism research while Igor Burstyn, Ph.D., far left, an associate professor of environmental and occupational health at the Drexel University, quipped, “Why do epidemiologists get all the hard questions?” Also pictured, left to right, are Serena Dudek, Ph.D., principal investigator in the NIEHS Laboratory of Neurobiology; Caroline Tanner, M.D., Ph.D., director of clinical research at the Parkinson’s Institute; and, Glenn Rall, Ph.D., associate professor at the Fox Chase Cancer Center. (Photo courtesy of Steve McCaw)

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Expert panel examines autoimmunity research

By Eddy Ball

An NIEHS meeting in Durham, N.C. Sept. 7-8 brought together an interdisciplinary group of experts to evaluate the state of the science regarding the role of the environment in the development of autoimmunity and related diseases. Organized and moderated by NIEHS Program Administrator Mike Humble, Ph.D., the meeting of approximately 40 NIEHS grantees and other experts also enjoyed generous support from the [American Autoimmune Related Diseases Association, Inc. \(AARDA\)](#), the leading national advocate for the more than 24 million Americans who suffer from autoimmune diseases.

For more than a decade, NIEHS has been a part of the trans-NIH Autoimmune Diseases Coordinating Committee, co-sponsored workshops, and funded research on the role of the environment in the development of autoimmune diseases (AD).

Identifying knowledge gaps in AD research

As Gwen Collman, Ph.D., interim director of the NIEHS Division of Extramural Research and Training (DERT), explained in her introductory comments, studies of twins and victims of



Mechanisms Group chair Patrick Leung, Ph.D., is an associate adjunct professor in the Division of Rheumatology, Allergy, and Clinical Immunology at the University of California, Davis. (Photo courtesy of Steve McCaw)

environmental emergencies, such as the World Trade Center attack, offer compelling presumptive evidence for a role of the environment in dysregulation of the immune response and the development of a wide range of diseases ([see text box](#)).

Although there is increasing support for gene-environment interactions as a cause of AD, Humble said, “There are still numerous gaps in knowledge in this field.” The expert panel meeting, he added, offers participants an opportunity “to explain to the world what we need to be doing.”

A comprehensive cross-disciplinary meta-analysis and needs assessment

NIEHS convened the expert panel to evaluate levels of confidence about existing research on the role of the environment in the development of autoimmune diseases and the directions future investigations should take, as well as foster productive relationships among the several disciplines involved in research. In addition to members of DERT, NIEHS representatives at the meeting included scientists involved in basic, clinical, and epidemiological research in the Division of Intramural Research and the National Toxicology Program.

Following months spent preparing white papers prior to the meeting, the writing and review panels worked in two breakout sessions to complete draft consensus statements on the strength of current data and study design. During the first breakout session, participants were assigned to one of four research-area groups — mechanisms, animal models, epidemiology and human data, and exposure assessment — to create 25-minute presentations of their key points based on the model made famous by the 2005 [Vallombrosa Consensus Statement on Environmental Contaminants and Human Fertility Compromise](#).

The next day, participants met in four integrated groups containing members from each of the research-area groups to tackle some of the overarching questions related to the role of the environment in the development of AD. They considered such topics as the adequacy of animal models in recapitulating AD in humans; the relative contributions of genetics, environment, and timing in the disease; the utility of *in vitro* and *in vivo* mechanistic studies; and the promise of new or existing approaches, such as biomarker development, epigenomic mapping, genome-wide association studies, biostatistical modeling, and disease registries.

Tangible outcomes of the expert panel deliberations

Following the meeting, writing groups will work on consensus statements that Humble said he expects to submit collectively for publication. Not surprisingly, the panelists agreed far more often than they differed, and



Discussing animal models, Scripps Research Institute investigator Michael Pollard, Ph.D., admonished his colleagues, “Future studies should be shaped by what happens in humans, not by what is possible in mice.” (Photo courtesy of Steve McCaw)



Referring to years of flat budgets ahead, Miller said, “Focusing the work to these most promising areas is more important than looking at everything.” He suggested that humanizing mice could make animal studies more relevant to understanding human disease. (Photo courtesy of Steve McCaw)

they uniformly called for more research and funding, as well as more effective integration of disciplinary approaches and methodologies.

In his remarks on day two, NIEHS Environmental Autoimmunity Group Principal Investigator [Fred Miller, M.D., Ph.D.](#), seemed to speak for many in the audience, as he praised meeting organizers for “forcing us to talk to people with different backgrounds.” He also seemed to express the group’s shared commitment to answering the important questions about AD. “We can’t let research momentum in understanding how autoimmune diseases develop stop at this point,” he urged. “Our goal is to identify better ways to predict and eventually prevent the development of some autoimmune diseases, because by the time we see obvious clinical disease, less can be done.”

Autoimmune disease — striking “like a thief in the night”

Autoimmunity is a result of a misdirected immune response that causes one’s own immune system to attack itself. Some of the more than [100 autoimmune diseases](#) listed by AARDA are lupus, type 1 diabetes, scleroderma, celiac disease, multiple sclerosis, Crohn’s disease, autoimmune hepatitis, rheumatoid arthritis, Graves’ disease, myasthenia gravis, myositis, antiphospholipid syndrome (APS), Sjogren’s syndrome, uveitis, polymyositis, Raynaud’s phenomenon, and demyelinating neuropathies.

As every presenter at the expert panel observed, the triggers, mechanisms, and timing of disease development remain largely unknown for the majority of ADs, despite numerous lines of experimental and epidemiological investigation. As Miller explained in his comments at the meeting, many ADs apparently develop long after whatever triggers them has laid the foundation for development of autoimmunity and ultimately the progressive development of the clinical criteria for diagnosing disease.

One possibly useful approach in future research, suggested [NIEHS grantee](#) and immunotoxicologist [Jean Pfau, Ph.D.](#), could be to determine the cluster of phenotypes that together make up patterns of AD, both for early signs of disease and to better utilize animal and *in vitro* models. Along with Pfau, several panelists also called for looking at shared patterns of mechanisms and outcomes of the many ADs, which have typically been recognized singularly as relatively rare disorders rather than within the overall category of autoimmunity.



NIEHS Epidemiology Branch Research Fellow [Christine Parks, Ph.D.](#), gave the *Exposure Assessment Group* report and stressed that complex exposures mean fine-tuning questionnaires for epidemiological studies. “One size doesn’t fit all,” she told the group. (Photo courtesy of Steve McCaw)



[Pat Mastin, Ph.D.](#), acting deputy director of the NIEHS extramural program, was one of five NIEHS scientists who served on the planning committee for the meeting. He worked with Humble, Miller, Parks, and NTP Immunology Discipline Leader [Dori Germolec, Ph.D.](#), to make the meeting a productive learning experience for everyone involved. (Photo courtesy of Steve McCaw)



NIEHS Somatic Hypermutation Group Principal Investigator [Marilyn Diaz, Ph.D.](#), center, contributed to the discussion of B cell activation in AD. (Photo courtesy of Steve McCaw)

New eye safety test methods proposed by interagency group

Submitted by Debbie McCarley

Over the next six months, federal regulatory agencies will consider adopting new test methods and strategies applicable to safety testing required to identify chemicals and products that may cause eye injuries. The [recommendations](#), including several *in vitro* safety testing methods and a testing strategy that does not require the use of animals, were developed by the [Interagency Coordinating Committee on the Validation of Alternative Methods \(ICCVAM\)](#), which is administered by a center that is part of the National Toxicology Program at NIEHS.



NIEHS/NTP Director Linda Birnbaum, Ph.D., forwarded the ICCVM recommendations Sept 7 on behalf of U.S. Secretary of Health and Human Services Kathleen Sebelius. ICCVAM, an interagency committee of the U.S. Federal government, is administered by the National Toxicology Program (NTP) Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM), directed by Rear Admiral William Stokes, D.V.M., who also serves as executive director of ICCVAM. The recommendations appear in an [announcement](#) published Sept. 17 in the Federal Register.

Members of the ICCVAM Ocular Toxicity Working Group are shown during a recent meeting. Shown in the front, left to right, are Donnie Lowther, U.S. Food and Drug Administration (FDA); Working Group Chair Jill Merrill, Ph.D., FDA; Marilyn Wind, Ph.D., former ICCVAM chair; and Jodie Kulpa-Eddy, D.V.M., U.S. Department of Agriculture, ICCVAM vice chair and acting chair. Shown in the back, left to right, are Masih Hashim, D.V.M., Ph.D., U.S. Environmental Protection Agency (EPA); Debbie McCall, EPA; John Redden, EPA; Meta Bonner, Ph.D., EPA; William Stokes, D.V.M., NICEATM director. (Photo courtesy of William Stokes)

“Routine use of the recommended pain management procedures for eye safety testing will ensure that animals are used in the most humane way possible, while providing information necessary to help protect the public from eye injuries that might result from chemicals and products,” Stokes explained. “Routine consideration and use of the *in vitro* methods where appropriate will also reduce animal use required for such testing.”

To protect workers and consumers, regulatory agencies require testing to determine if chemicals and products may cause temporary or permanent eye injuries such as blindness. Each year, approximately two million eye injuries occur in the U.S., of which more than 40,000 result in permanent visual impairment. Household cleaning chemicals and other chemical products are the leading cause of consumer product-related eye injuries in children under age 10. Adoption and implementation of the ICCVAM recommendations are expected to support continued protection of public health, while contributing to more humane and reduced animal use for required product safety testing.

ICCVAM recommended that pain management procedures should always be used whenever it is necessary to use rabbits for eye safety testing required by federal regulatory agencies. The ICCVAM evaluation report includes a test method protocol that describes how to use topical anesthetics, similar to those used in human eye surgeries, and systemic analgesics prior to and after test substance administration in order to avoid or minimize

animal pain and distress. The report also identifies specific clinical signs and lesions that, if observed during animal testing, can be used as humane endpoints to allow the investigator to end a study early in order to reduce or avoid potential animal pain and distress.

The current recommendations are the latest from a series of NICEATM and ICCVAM evaluations of non-animal test methods for identifying potential eye injury hazards. In 2008, federal agencies accepted the first two *in vitro* test methods recommended by ICCVAM that can be used to identify substances that cause the most severe eye injuries without the use of animals. All federal agencies also accepted or endorsed the ICCVAM recommendations. These recommendations were used to develop international test guidelines that were adopted last year by the 32 member countries of the Organisation for Economic Co-operation and Development.

Federal agencies must respond regarding their acceptance of the current ICCVAM test method recommendations within 180 days.

(Debbie McCarley is the special assistant to Rear Admiral William Stokes, D.V.M., D.A.C.L.A.M., director of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods.)

ICCVAM recommendations

The ICCVAM and the Ocular Toxicity Working Group (OTWG) developed the recommendations with scientific support from NICEATM.

The OTWG is chaired by Jill Merrill, Ph.D., of the Food and Drug Administration (FDA) and includes scientists from the U.S. Consumer Product Safety Commission, the U.S. Department of Defense, the U.S. Department of Transportation, the U.S. Environmental Protection Agency, FDA, NIEHS, and the Occupational Safety and Health Administration.

Several NIEHS scientists serve on the working group and contributed to the ICCVAM evaluations and recommendations, including Warren Casey, Ph.D., Mark Cesta, D.V.M., Buck Grissom, Ph.D., and William Stokes, D.V.M.

The ICCVAM test method evaluation reports, which contain the complete ICCVAM recommendations, are available on the NICEATM–ICCVAM Website. Along with an [overview](#) of the ICCVAM evaluation of ocular safety testing methods, this site contains links to pages with more detailed information on each of the ICCVAM evaluations of ocular toxicity test methods, including test method evaluation reports.

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European Teratology Society honors NIEHS-led research

By Melissa Kerr

A study funded by an interagency agreement between NIEHS and the U.S. Food and Drug Administration (FDA) was honored as Paper of the Year at the European Teratology Society (ETS) annual conference Sept. 5-8 in Barcelona, Spain.

NIEHS Staff Scientist Retha Newbold was principal investigator and senior author on the [study](#). First author Barry Delclos, Ph. D., an FDA National Center for Toxicological Research (NCTR) pharmacologist, presented an Elsevier Award lecture based on the research.

The Elsevier Award is an honor given to authors of the paper selected by [ETS](#) council members as the best paper published in the journal [Reproductive Toxicology](#) the previous year.

Expanding on research initiated by the National Toxicology Program (NTP), the study examined multiple generations and collected data on chronic toxicity and reproductive effects of exposure to genistein and ethinyl estradiol (EE2). The study was an effort to address aspects of the endocrine disruptor hypothesis, which emerged from work on diethylstilbestrol (DES), a synthetic estrogen that is well established as a cause of several adverse effects in both sexes, including carcinogenesis.

According to the endocrine disruptor hypothesis, there are other chemicals in the environment that are weaker estrogens than DES, but could still have the potential to cause similar adverse effects in both human and wildlife populations.

Genistein is a phytoestrogen found commonly in soy-based foods, dietary supplements and infant formulas. EE2 is a bio-active estrogen used in almost all modern oral contraceptive pill formulas and is also found as an environmental contaminant. The experiments spanned five generations and compared the similar and different adverse effects observed by feeding the test subject the two different chemicals at several dose levels.

According to the study report, both EE2 and genistein in high doses showed similar effects in continuously exposed female rats, “including decreased body weights, accelerated vaginal opening, and altered estrous cycles in young animals.” Genistein-treated animals showed a reduction in litter size, while EE2 significantly increased the occurrence of uterine lesions. The offspring of succeeding generations of exposed animals also showed some of the effects. The relevance of the findings to human exposure situations is unknown at this point.

It was the first time Delclos had attended the annual meeting. “I found it to be an interesting meeting,” he said, “conducive to open discussion and exchange of ideas.” According to the Society’s Website, the objectives of ETS are to stimulate interest in and promote the sharing of ideas and information about the causes and prevention of adverse effects on reproduction and development. The conference, held in conjunction with the European Network of Teratology Information Services (ENTIS), explored the causes and prevention of birth defects in Europe.

Delclos said he enjoyed working with and learning from Newbold. He explained, “The most important thing to me [about the award] is that the hard work of the many individuals involved in the planning and conduct of these studies, both here at NCTR and at NTP, was acknowledged.”

Citation: Delclos KB, Weis CC, Bucci TJ, Olson G, Mellick P, Sadovova N, Latendresse JR, Thorn B and Newbold RR. 2009. Overlapping but distinct effects of genistein and ethinyl estradiol (EE(2)) in female Sprague-Dawley rats in multigenerational reproductive and chronic toxicity studies. *Reprod Toxicol* 27(2): 117-132.

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)



Principal Investigator Newbold is a veteran NIEHS researcher and a pioneer in the research of endocrine disrupting compounds in the environment and their effects on human health and development. (Photo courtesy of Steve McCaw)

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This month in EHP

The October issue of *Environmental Health Perspectives* (EHP) is the journal's 13th annual Children's Health Issue. Feature articles elaborate on the theme by addressing "Growing Knowledge: Using Stem Cells to Study Developmental Neurotoxicity" and "Dietary Iodine: Why Are So Many Mothers Not Getting Enough?" The issue also contains twelve scientific studies focusing on children's health, along with studies on other environmental health topics.

In this month's [podcast](#), host Ashley Ahearn talks with occupational and environmental epidemiologist Manolis Kogevinas, M.D., Ph.D., about his research on the health effects of swimming in chlorinated pools.

Among the research studies included in this issue are:

- Research Recommendations for 20 Carcinogens
- Urban Form and Extreme Heat Events
- Vaccination Response after Exposure to PCBs
- PBDEs and Thyroid Hormone During Pregnancy
- Health Effects of Unflued Gas Heaters in Classrooms

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<http://twitter.com/ehponline>



Steven Zeisel to give Hans L. Falk Memorial Lecture

By Angelika Zaremba

Steven Zeisel, M.D., Ph.D., will present the annual Hans L. Falk Memorial Lecture Oct. 4 at the NIEHS Rodbell Auditorium in Research Triangle Park, N.C. NIEHS/NTP Director Linda Birnbaum, Ph.D., will host his presentation, "Nutrigenomics, estrogen, and environmental chemicals influence the dietary requirement for choline."

[Zeisel](#) is the Kenan Distinguished University Professor in the Department of Nutrition and Pediatrics at the University of North Carolina at Chapel Hill (UNC-CH) Gillings School of Global Public Health and UNC School of Medicine, as well as director of the UNC Nutrition Research Institute (NRI) in Kannapolis, N.C. He serves as the principal investigator on multiple federally funded research projects that focus on human nutrition research and specifically on human requirements for choline.

Using new approaches in nutrigenomics and metabolomics in studies of humans, mice, and cells, Zeisel's group is working to identify the mechanisms underlying individual nutritional variations and needs. Zeisel is credited with discovering the role of choline as a dietary methyl donor and essential nutrient, and he has studied its need by women during pregnancy. His team showed that choline influences epigenetic modulation during fetal development. As an essential nutrient, it is also needed for healthy muscle and liver function.

Choline can be derived from the diet and is found in different concentrations in a variety of foods, but it can also be synthesized endogenously. Using choline as a model to study individual differences in nutritional requirements, the group identified an estrogen-dependent induction of choline synthesis.

Zeisel's group discovered that half of the young women they studied have common genetic variants that make them unable to synthesize enough choline endogenously to meet their requirements. Older women and men need a choline-rich diet to prevent liver and muscle damage.

Held each year in honor of the Institute's first scientific director, Hans Falk, Ph.D., the memorial lecture series features distinguished guest speakers who have made significant contributions to environmental health science research. Falk was one of the founding members at NIEHS and is recognized internationally as a pioneer in the environmental health sciences.

(Angelika Zaremba, Ph.D., is a visiting postdoctoral fellow in the NIEHS Laboratory of Signal Transduction Inositol Signaling Group.)

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Zeisel has been honored many times for his work on human nutrition research, and his discoveries are helping scientists understand individual nutrient needs and reduce the risk of disease. (Photo courtesy of UNC-CH)

Extramural papers of the month

By Jerry Phelps

- [Amplifying stem cells](#)
- [Low dose BPA alters gene expression in the fetal mouse ovary](#)
- [Common genetic variants associated with blood lipids](#)
- [Charlotte, NC light rail transit use reduces obesity risk](#)



Read the current Superfund Research Program [Research Brief](#). New issues are published on the first Wednesday of each month.

Amplifying stem cells

The success of hematopoietic stem cell transplantation into human patients for treating blood diseases depends on the number of stem cells in the graft. Culturing stem cells with a cocktail of growth factors before transplantation can induce proliferation, but the increase in cell number is rapidly followed by differentiation, which is accompanied by loss of the cell surface markers CD34 and CD133.

NIEHS grantees recently identified the purine derivative StemRegenin 1 (SR1) in a screen for small molecules that could stimulate stem cell growth without hastening differentiation. Culturing human stem cells collected from peripheral blood with a cytokine cocktail plus SR1 increased the number of CD34+ and CD133+ cell populations as compared to control cells treated with the growth factors alone and also increased the number of multilineage colonies formed by stem cells. SR1 treatment increased both short- and long-term engraftment of human umbilical cord blood CD34+ cells into mice as compared to uncultured or control stem cells cultured with cytokines alone.

SR1 inhibited the aryl hydrocarbon (Ah) receptor, a nuclear receptor that has been implicated in pathways that regulate hematopoiesis. The authors conclude that modulating Ah receptor activity may be a useful strategy for improving clinical outcome of stem cell transplantation.

Citation: Boitano AE, Wang J, Romeo R, Bouchez LC, Parker AE, Sutton SE, et al. 2010. Aryl hydrocarbon receptor antagonists promote the expansion of human hematopoietic stem cells. *Science* 329(5997):1345-1348.

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Low dose BPA alters gene expression in the fetal mouse ovary

A research team led by NIEHS grantee Patricia Hunt, Ph.D., at Washington State University reports that gene expression changes in fetal mouse ovaries occur as soon as 12 hours after the mother has been exposed to bisphenol A. These changes may produce adverse reproductive outcomes as the mice grow and develop.

Bisphenol A is a ubiquitous chemical found in many forms of plastic that humans come in contact with daily. A growing body of evidence demonstrates that it is an endocrine disruptor at all stages of life.

The research shows that bisphenol A affects the earliest stages of egg production in the ovaries of developing mice fetuses, suggesting that their offspring may suffer genetic defects in biological processes such as mitosis and DNA replication. This is an example of a transgenerational effect, in that the grandchildren of the exposed animals will be at risk for adverse health effects.

The research team also reports finding down-regulation of mitotic or cell cycle genes raising the possibility that bisphenol A exposure might act to shorten the reproductive lifespan by reducing the pool of fetal oocytes that later mature into eggs. If this effect is true in humans, it could result in premature menopause in women.

Citation: Lawson C, Gieske M, Murdoch B, Ye P, Li Y, Hassold T, Hunt PA. 2010. Gene Expression in the Fetal Mouse Ovary Is Altered by Exposure to Low Doses of Bisphenol A. *Biol Reprod*. Epub ahead of print. DOI: 10.1095/biolreprod.110.084814.

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Common genetic variants associated with blood lipids

A genome-wide association study partially supported by NIEHS reports genetic variants associated with levels of four blood lipids — total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides. The paper is a worldwide multi-institute collaborative effort based on data from more than 100,000 individuals of European descent.

Additional analyses were undertaken in populations of East Asian, South Asian, and African American ancestry using a different cohort of Europeans as a control group. The single nucleotide polymorphisms found in this control European cohort were largely replicated in the non-European populations, albeit to a lesser extent in the African American population.

In order to assess the clinical relevance of these loci, associations with coronary artery disease were assessed in 25,000 cases and 66,000 controls of European descent. Thirteen loci showed association, with most of them also being associated with low-density lipoprotein, showing a causal risk factor. A second clinical phenotype, hyperlipidaemia, was also assessed in a smaller study, where individuals with greater numbers of risk loci showed higher lipid levels.

The study identifies a large number of loci associated with blood lipids in both European and non-European populations, as well as provides clinical and biological evidence that increases the strength of these associations.

Citation: [Teslovich TM, Musunuru K, Smith AV, Edmondson AC, Stylianou IM, Koseki M, et al. 2010. Biological, clinical and population relevance of 95 loci for blood lipids. Nature 466\(7307\):707-713.](#)

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Charlotte, NC light rail transit use reduces obesity risk

New research findings supported solely by NIEHS as part of its built environment grant portfolio demonstrate that increasing the availability of light rail systems and improving neighborhood environments is associated with a reduction in body mass index.

Researchers conducted two surveys in Charlotte, NC, before and after the completion of a light rail system serving downtown locations. The surveys assessed levels of physical activity, body mass index, perception of neighborhood environments, and the use of public transit systems. They found that construction of the light rail system led to increases in walking and subsequent weight loss. These findings were also associated with having a positive impression of one's neighborhood. The use of the light-rail system to commute to work resulted in an average reduction in body mass index of 1.18 kilogram per meter squared and an 81 percent decreased risk of becoming obese.

Citation: [MacDonald JM, Stokes RJ, Cohen DA, Kofner A, Ridgeway GK. 2010. The effect of light rail transit on body mass index and physical activity. Am J Prev Med 39\(2\):105-112.](#)

(Jerry Phelps is a program analyst in the NIEHS Division of Extramural Research and Training.)

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Intramural papers of the month

By Jeffrey Stumpf and Negin Martin

- [Estrogen increases chemical uptake by brain](#)
- [Base damage of single-stranded DNA intermediate causes localized hyper-mutability in budding yeast](#)
- [Genetic biomarkers for early diagnosis of lung cancer](#)
- [Eosinophil peroxidase reacts with sulfite to form protein radicals](#)

Estrogen increases chemical uptake by brain

A collaboration between scientists from NIEHS and the University of Minnesota Duluth has led to the discovery of a new mechanism by which estrogen regulates blood-brain barrier permeability in the rodent brain. Based on their findings, co-administration of estrogen offers a possible new strategy for delivering chemotherapeutics to cancer cells in the brain.

The blood-brain barrier is a physiological network that protects the brain from chemicals that circulate in blood, but this system also prevents therapeutic agents from reaching and interacting with tumor cells in the brain. The investigators knew that the breast cancer resistant protein (BCRP) present in the capillaries acted as an efflux pump, limiting the brain's uptake of drugs. When team members examined brain capillaries from rodents treated with estrogen, they found that BCRP had been internalized and degraded. They speculated that loss of BCRP should alter the blood-brain barrier to increase brain penetration of certain therapeutic drugs.

This work showed that estrogen signaling at the blood-brain barrier is accomplished through estrogen receptor beta (ERbeta) and activation of the phosphatase and tensin homolog (PTEN) pathway. The signal is transmitted within minutes and does not include the canonical transcriptional activation by the nuclear receptor ERbeta. This research could potentially allow physicians to improve the delivery of chemotherapeutics to the central nervous system, thereby improving the treatment of brain tumors.

Citation: [Hartz AM](#), [Madole EK](#), [Miller DS](#), [Bauer B](#). 2010. Estrogen receptor beta signaling through phosphatase and tensin homolog/phosphoinositide 3-kinase/Akt/glycogen synthase kinase 3 down-regulates blood-brain barrier breast cancer resistance protein. *J Pharmacol Exp Ther* 334(2):467-476.

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Base damage of single-stranded DNA intermediate causes localized hyper-mutability in budding yeast

A study from the Chromosome Stability Group at NIEHS demonstrates that the generation of several kilobase regions of single strand DNA (ssDNA) dramatically increases the likelihood of mutations, a phenomenon called localized hyper-mutability (LHM). The paper reports that exposure to the alkylating agent methyl methanesulfonate causes a 20,000-fold increase in mutations near an induced double-strand break (DSB) in budding yeast.

LHM is proposed to occur when ssDNA is exposed to DNA damaging agents resulting in mutagenic replication of irreparably damaged bases. The ssDNA regions are transient intermediates during DSB repair. Therefore, during DSB repair, the adjacent DNA becomes vulnerable to increased mutagenesis. The mutations mostly result from copying of ssDNA-specific methylated lesions of cytosine by DNA pol zeta, a polymerase that often performs error-prone translesion DNA synthesis.

Mutations are an important source of improved evolutionary fitness, as well as precursors for cancer and genetic disease. The increase in mutations needed to drive these processes are thought to be too large to maintain viability, if the mutagenesis is randomly distributed across the genome. The clustered nature of LHM can provide drastic changes to small regions of DNA including multiple changes in single genes, while maintaining overall genome stability.

Citation: [Yang Y](#), [Gordenin DA](#), [Resnick MA](#). 2010. A single-strand specific lesion drives MMS-induced hyper-mutability at a double-strand break in yeast. *DNA Repair (Amst)* 9(8):914-921.

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Genetic biomarkers for early diagnosis of lung cancer

NIEHS researchers have developed a method for identifying single nucleotide polymorphisms (SNPs) in the human genome that may contribute to lung cancer by affecting gene expression.

Chronic exposure to cigarette smoke severely injures airway cells yet only 10 to 15 percent of smokers develop lung cancer, suggesting a role for genetic variation in susceptibility. In collaboration with Avrum Spira, M.D., of Boston University School of Medicine, NIEHS researchers obtained samples from patients being screened for lung cancer. Global gene expression was assessed in normal airway cells obtained by bronchoscopy from smokers who developed lung cancer, smokers without lung cancer, and never smokers. Using bioinformatics analysis, differences in NRF2-mediated antioxidant pathway gene expression were observed among these groups and a key role was identified for MAFG, a binding partner of NRF2.

Hypothesizing that SNPs could contribute to gene expression variability, SNPs in NRF2 binding sites were compared with gene expression. Several SNPs were associated both with gene expression and with cancer status, suggesting that these SNPs could influence expression, and that expression might influence the development of cancer.

While limited in scope, this work demonstrates a general approach that integrates bioinformatics analysis of pathways and transcription factor binding sites with genotype, gene expression and disease status, to identify polymorphisms affecting individual differences in gene expression and disease risk.

Citation: Wang X, Chorley BN, Pittman GS, Kleeberger SR, Brothers J 2nd, Liu G, et al. 2010. Genetic variation and antioxidant response gene expression in the bronchial airway epithelium of smokers at risk for lung cancer. PLoS One 5(8):e11934.

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Eosinophil peroxidase reacts with sulfite to form protein radicals

NIEHS scientists reported in the Journal of Biological Chemistry that sulfites, hydrated sulfur dioxide, cause oxidative damage to proteins. The study showed that proteins are damaged upon exposure to reactive molecules called free radicals that form during the oxidation of sulfites by eosinophil peroxidase (EPO).

Sulfites are converted to the sulfur trioxide radical by EPO and are further oxidized to form peroxymonosulfate and sulfate anion radicals. Using cell culture cells that produced EPO and detection of trapped radicals in a stable compound by using the spin trap called DMPO, the researchers demonstrated the presence of these reactive radical species and the oxidation of human serum albumin and EPO itself, implying that many other proteins may potentially suffer oxidative damage.

In addition to air pollution, sulfites are found in preservatives, bleaching agents, and various medications. In the United States, approximately 500,000 individuals are sensitive to sulfite-containing products. Although the mechanism is unknown, toxic levels of sulfites cause allergic reactions similar to those experienced during asthma attacks. Because EPO is secreted by white blood cells, this study raises the possibility that protein damage by free radicals contributes to tissue injury in inflammation and other immune responses.

Citation: Rangelova K, Chatterjee S, Ehrenshaft M, Ramirez DC, Summers FA, Kadiiska MB, et al. 2010. Protein radical formation resulting from eosinophil peroxidase-catalyzed oxidation of sulfite. J Biol Chem 285(31):24195-24205.

(Jeffrey Stumpf, Ph.D., is a postdoctoral fellow in the NIEHS Laboratory of Molecular Genetics Mitochondrial DNA Replication Group. Negin Martin, Ph.D., is a biologist in the NIEHS Laboratory of Neurobiology's Viral Vector Core.)

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Inside the Institute

NIEHS celebrates Women's Equality Day

By Eddy Ball

The long struggle for equal voting rights for women was at center stage Aug. 26 at NIEHS as Noreen Gordon addressed “The Effect of the 19th Amendment on American History/*Herstory*: A Socioeconomic Perspective,” celebrating the 90th anniversary of its ratification. Since April, Gordon has served as the on-site labor and employee relations specialist for NIEHS, representing the Institute in labor contract negotiations and carrying out her duties as part of the NIH Office of Human Resources Workforce Relations Division.

The union at NIEHS, American Federation of Government Employees (AFGE) Local 2923, hosted the precedent-setting event. In his opening remarks, AFGE Local 2923 President Bill Jirles described the celebration as a first in two important ways. “One of them is because this is the first tribute to Women’s Equality Day here at NIEHS,” Jirles explained, “and the other because this is the first partnership activity of this kind between the union and NIEHS management.”

Roots in the abolitionist movement

In her enthusiastic survey of the struggle for women’s voting rights, Gordon began with what historians consider the movement’s seminal document, the [1848 Seneca Falls Declaration of Sentiments](#), and traced the 72-year history of what she called “a long and uphill battle through the sacrifices of many” to achieve passage and ratification of the 19th Amendment. Although American women, including Abigail Adams, wife of President John Adams, had long appreciated the irony of the Constitution’s idealistic phrase “we the people” juxtaposed with the legislated exclusion of women from equal rights, Gordon noted that it was the anti-slavery movement that finally brought the struggle to national attention and offered women a venue for voicing their concerns about inequality.



Gordon called the ratification of the 19th Amendment the result of “the only non-violent revolution in this country’s history.” (Photo courtesy of Steve McCaw)



Reflecting on the brave women who spoke out for their voting rights, Jirles encouraged members of the audience “to think about how we use our voice” to improve our lives. (Photo courtesy of Steve McCaw)

Gordon's narrative was rich in detail about the heroines of the struggle — such women as Elizabeth Cady Stanton, Lucretia Mott, Sojourner Truth, Susan B. Anthony, Lucy Stone, and Julia Ward Howe. She described the arguments that surrounded the 13th, 14th, and 15th Amendments, as human rights advocates were divided on the benefits of guaranteeing rights for former slaves, compared to holding out for an amendment that would also bring true equality for women. Divisions also developed among women's rights groups, Gordon said, over the issue of expediency and enabling measures versus persisting in demands for an unequivocal guarantee of equal voting rights.

Racial and economic implications

Taking her discussion beyond the ratification of the 19th Amendment, Gordon surveyed the voting rights struggle in terms of racial equality, as women of color joined their male counterparts in a bid for full participation in elections nationwide and economic equality. Gordon also discussed the contributions of former U.S Representative Bella Abzug, who spearheaded the Women's Equality Day resolution of 1971, the National Organization for Women, and the Equal Rights Amendment.

As she neared the end of her presentation, Gordon assured her listeners, "The struggle continues." Today, she explained, more women than men in most age groups turn out to vote in each election, but the number of elected representatives shows that progress still needs to be made. Currently, 17 women serve in the U.S. Senate and 74 sit in the U.S. House of Representatives — important advances, Gordon conceded, but still far from a true reflection of the proportion of women in the U.S. population.

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Several men came out to celebrate equal voting rights for women, including NIEHS Office of Management employees and union stewards Versal Mason, right foreground, and Clarence Gibson. (Photo courtesy of Steve McCaw)

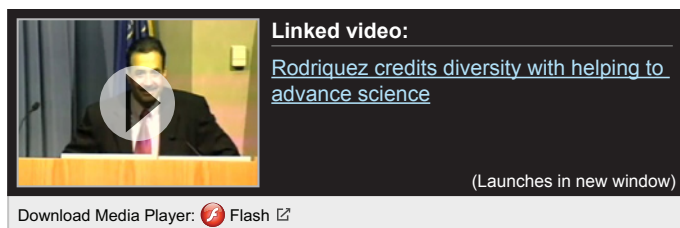


Jirles, left, presented Gordon with a copy of the poster announcing the first NIEHS tribute to Women's Equality Day. Jirles and Gordon will share another important document as they negotiate the new contract between NIEHS and AFGE Local 2923. (Photo courtesy of Steve McCaw)

Exploring the origins of American medicine

By Eddy Ball

NIH celebrated Hispanic heritage Sept. 21 with an engaging talk by Eloy Rodriguez, Ph.D., the James A. Perkins Professor in ethnobotanical medicine and biochemistry at Cornell University. The presentation, videocast from the NIH campus in Bethesda, Md., combined an historical review of natural medicines and medicinal foods in the New World with an appeal for overcoming health disparities with a health and science workforce that better represents the diversity of the American population.

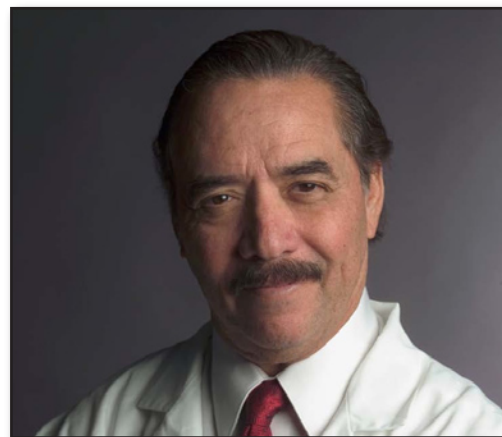


Rodriguez's audience included NIH employees and a contingent of students from nearby Wheaton High School in Silver Spring, Md. Since one of Rodriguez's themes was training the next generation of Hispanics to participate in a diverse scientific workforce, he addressed the young people in his audience directly several times during his lively and engaging presentation.

In the course of his talk, [Rodriguez](#) appealed to young people with several photos of his undergraduate and graduate students and stories about their successful scientific careers. He also shared stories of his family — both the successes of his 64 cousins, and aunts and uncles, as well as the untimely deaths of family members from complications of diabetes.

Telling his listeners, "I get knowledge from the people," Rodriguez took his audience back to the roots of American medicine among indigenous peoples, especially the herb-savvy women who were using plants and foods as medicine long before Columbus stumbled across the Americas. "The history of science goes way, way back, even before the coming of the Europeans," he explained.

Pointing to such plants as Clitoria, a flower used to treat malaria, and Heliotropium, which supplies a juice used topically on breast tumors, Rodriguez praised the vast healing knowledge of so-called primitive peoples in South and Central America. He also described the healing qualities of indigenous foods, such as chili and mole, as well as the way that Europeans and African slaves contributed to the creation of a diverse medicine in the New World.



Rodriguez closed his discussion of health disparities by referring to a famous quote by Woody Allen — "I don't want to achieve immortality through my work... I want to achieve it through not dying." (Photo courtesy of Eloy Rodriguez)



In his comments, Roman referred to the 2010 National Hispanic Heritage Celebration theme — "Heritage, Diversity, Integrity and Honor: The Renewed Hope of America." (Photo courtesy of Steve McCaw)



Collins, above, thanked Roman and the Hispanic Employment Committee and reaffirmed the NIH commitment to diversity and eliminating health disparities. (Photo courtesy of NIH)

In the final part of his talk, Rodriguez turned to the topics of health disparities and workplace diversity. “Am I outraged?” he asked rhetorically. “Of course, I’m outraged. We cannot afford to let these health disparities persist.” He pointed to the 2.9 percent of the NIH workforce that is Hispanic — at a time when Hispanics represent 16 percent of the American population — and the absence of Hispanics among senior scientists. He said simply, but dramatically, “This can’t be.”

NIH Hispanic Employment Program Manager Gerard Roman, who is based at NIEHS, introduced the program on behalf of the NIH Hispanic Employment Committee and NIH Office of Equal Opportunity and Diversity Management (OEODM). NIH leadership speaking at the event included Director Francis Collins, M.D., Ph.D., National Institute on Drug Abuse Director Nora Volkow, M.D., and OEODM Director Lawrence Self.

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Employees honored for years of service

By Eddy Ball

NIEHS held its second annual Years of Service Awards Ceremony Aug. 27 in Rodbell Auditorium. NIEHS/NTP Director Linda Birnbaum, Ph.D., recognized employees who have reached important milestones in their federal service, celebrating 10th, 20th, 30th, and 40th anniversaries, as well as recent retirements.

According to Birnbaum, NIEHS honored a total of 1,110 years of service at the celebration. “It takes a unique type of person to succeed in government,” she said. When she initiated the first Years of Service Awards Ceremony in 2009, Birnbaum told the awardees, “Years of service is certainly an important achievement, and it should be singled out for recognition.”

Assisted by NIEHS Acting Deputy Director Steve Kleeberger, Ph.D., and NIEHS Chief of Staff Paul Jung, M.D., Birnbaum handed out certificates to employees as honorees came to the stage for a photograph with her. At the conclusion of the ceremony, Kleeberger turned the tables on Birnbaum as he presented her with an unexpected certificate of her own for 30 years of federal service.

The leaders joined honorees and their guests at an ice cream and cake reception afterwards in the main lobby of the Rall Building.



Volkow, above, summarized Rodriguez’s many accomplishments in her introduction of the speaker. (Photo courtesy of NIH)



Birnbaum’s exuberance was infectious, as she praised employees for their longevity and dedication. (Photo courtesy of Steve McCaw)

Employees and their milestones

10 YEARS

Blankenship-Paris, Terry
Bushel, Pierre
Chandler, Novella (Colleen)
Chrysovergis, Kaliopi (Kali)
Clayton, Natasha
Dimes, Martha
Ehrenshaft, Marilyn
Fender, Margaret (Meg)
Goulding, David
Harris, Patricia
Hite, Sharon
Lawler, Cindy
Longley, Matthew
Lunn, Ruth
Madenspacher, Jennifer
McPherson, Christopher
Peddada, Shyamal
Pinto, Audrey
Sever, Michelle
Sobhany, Hooramack (Mack)
Stefanick, Donna
Sutton, Deloris
Trotter, Kevin
Tucker, Charles (CJ)
Wells, Monya
Whiteside, Tanya
Wilson, Deborah (Debbie)

20 YEARS

Akiyama, Steven
Allen, Janice
Bass, Linda
Bell, Douglas
Bowden, Florence (Beth)
Dearry, Allen
Edwards, Lori
Fields, Sally
Flowers, Carolyn
Haugen, Astrid
Hughes, Joseph (Chip)
Jeter, Shawn
Kadiiska, Maria
Levine, Robert (Rob)
Locklear, Jacqueline
Lynn, Andrea
Paules, Richard (Rick)
Reinlib, Leslie (Les)
Solomon, Gregory
Thigpen Tart, Kimberly
Withers, Sheila
Zeldin, Darryl

30 YEARS

Caviness, Adolphus (Al)
Fitzgerald, William (Bill)
Greenwell, Arnold
Hong, Hue-Hua (Lily)
Lambert, Jane
McGrew, Laura
Pagan, Georgina (Georgie)
Thompson, Claudia

40 YEARS

Chhabra, Rajendra (Raj)
Hawkins, Thomas (Tom)
Larry Judd
Willis, William (Bill)
Wilson, Ralph

RETIRED

Anna, Colleen
Boyd, Nell
Champion, Larry
Corbett, Barbara (Jean)
Crawford, Diane
Grigston, Vicky
Lindley, Linda (Lin)
Maghan, Leona
McCants, Rene
Robertson, William (Dav)
Shane, Barbara
Stasiewicz, Stanley (Stan)
Sykes, Destiny



*Just when she thought it was high time for cake and ice cream, Birnbaum found herself on the receiving end as Kleeberger, right, presented her with a surprise — an award for her own 30 years of government service.
(Photo courtesy of Steve McCaw)*



Colleagues Trish Castranio, left, and Mack Sobhany enjoyed refreshments following the ceremony. Sobhany was recognized earlier for his decade of service. (Photo courtesy of Steve McCaw)



Awardee Pierre Bushel joined Lewin Liu, left, and Cindy Innes, right, at the reception in the Rall Building lobby. (Photo courtesy of Steve McCaw)

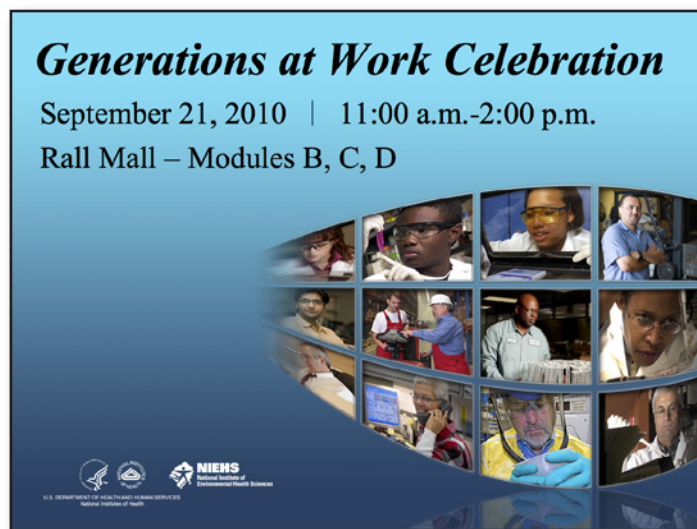
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Generations at Work Celebration spotlights families

By Melissa Kerr

To foster employee work/life balance, the NIEHS Employee Services office presented a Generations at Work Celebration Sept. 21 in conjunction with the [Research Triangle Chapter of Blacks In Government \(BIG\)](#) Annual Fish Fry. Twenty-nine community organizations, businesses, and NIEHS organizations set up tables lining the Rall Building Mall area. Work/Life events of this kind are a tradition at NIEHS and always include freebies, such as a complimentary bag to hold the various fliers, candy, calendars, and other giveaways that visitors pick up as they visit the booths.

Representatives of the businesses and groups spoke with employees about services that could assist them and their families at every stage of life, from infancy to retirement. From organizations within NIEHS, event-goers were able to get information concerning alternate forms of transportation and how to become a flexitarian by adopting a diet with reduced meat intake, as well as about more ergonomic work environments to help promote health and safety. Advocacy groups, such as those representing persons with disabilities, were also on hand to discuss their programs.



The Generations at Work poster highlighted the diversity of the NIEHS work force and the many roles they play in the Institute's work. (Poster courtesy of Dona McNeill)

NIEHS Employee Services hosted many service groups, including the [North Carolina Library for the Blind and Physically Handicapped](#), a special public library for people who cannot use regular printed materials; [Marbles Kids Museum](#), a hands-on museum that promotes learning through play; and the [Center for Universal Design](#), which promotes the belief that built environments and products can be made usable by people of all ages and abilities.

Employee Services Manager [Dona McNeill](#) said she has “never been disappointed in the way invited organizations share information about themselves and their services.” As she explained, NIEHS Work/Life events evolve from year to year, and it is never the same event twice. This year was the first time McNeill and co-organizer intern [Jenn Evans](#) collaborated with a number of organizations across NIEHS, including the Office of Management, the Diversity Council, the Disability Advocacy Committee, the American Federation of Government Employees, and BIG.

(Melissa Kerr studies chemistry at North Carolina Central University. She is currently an intern in the NIEHS Office of Communications and Public Liaison.)



NIEHS staffers J.J. Bell-Nichols, left, and Elizabeth Ruben were on hand at the Combined Federal Campaign booth to tell visitors how to give back to the community and target charitable contributions to local groups. (Photo courtesy of Ed Kang)



A Work/Life event just wouldn't be complete without an alternate transportation table. NIEHS employees Dick Sloane, left, and Rachel Gross discuss programs the Institute offers to promote use of public transportation and carpooling. (Photo courtesy of Ed Kang)



Outside on the patio, BIG members served fried fish and sides to hungry visitors. Shown above, left to right, are Veronica Godfrey Robinson of NIEHS, Terry Jones of U.S. Citizenship and Immigration Services, and Wanda Holliday of NIEHS. (Photo courtesy of Steve McCaw)



In what may be the beginning of a mutually beneficial relationship, Employee Services and BIG synchronized their annual events this year and maximized attendance at both. (Photo courtesy of Steve McCaw)

NIEHS Chief of Staff Paul Jung, M.D., savored his first BIG fish fry since joining NIEHS earlier this year. If Jung's smile is any indication, it's a safe bet that he'll be back next year. (Photo courtesy of Steve McCaw)

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